UNIVERSITY OF MICHIGAN
SEP 25 1950
MEDICAL LIBRARY

INTERNATIONAL CONGRESS OF INTERNAL MEDICINE

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY SEPTEMBER 9 1950

TABLE OF CONTENTS

Nature of the Intrinsic Factor of Castle BYRON E. HALL, M.D. 585
Cortisone (Compound E) J. M. CARLISLE, M.D. 590
Streptomycin and Neomycin SELMAN A. WAKSMAN, Ph.D. 595
Sulphonamides for Mixture Therapy DAVID LEHR, M.D. 601
Medical Treatment of Hydatid Cysts of Lung MARIANO R. CASTEX, M.D., and EDUARDO L. CAPDEHOURAT, M.D. 604
Advances in Knowledge of the Malaria Parasite H. E. SHORTT, C.I.E., M.D., F.R.S. 606

MEDICAL MEMORANDA

Death from Atropine Poisoning. W. E. HEATH, M.B., B.S., D.O. 608
Neurological Complication after Combined Diphtheria and Pertussis Immunization. J. VAHRMAN, M.B., B.S., C.P.H. 608
An Emergency Leucotomy. M. O'C. DRURY, M.D., D.P.M. 609

REFRESHER COURSE

Chemotherapy—II. Indications for Use of Penicillin. LAWRENCE P. GARROD, M.D., F.R.C.P. 617

GENERAL ARTICLES AND NEWS

CREMATION 619
WORLD FEDERATION FOR MENTAL HEALTH 620
MEDICO-LEGAL 633
MEDICAL NEWS 635
QUESTIONS AND COMMENTS 637

OBITUARY

Sir Reginald St. Johnston, K.C.M.G., M.R.C.S. 631
A. D. Macpherson, M.B. 631
M. B. Ray, D.S.O., O.B.E., M.D. 632
A. Christie Reid, M.D. 632
F. J. Strong Heaney, M.D., F.R.C.S.I. 632
W. A. Milligan, M.D., F.R.C.S.Ed. 632

REVIEWS

Postgraduate Lectures 610
Classification of Shigellae 610
The Statistician's Job 610
Occupational Therapy 610
Foot Disorders 611

LEADING ARTICLES

International Congress of Internal Medicine 612
Pernicious Anaemia and the Intrinsic Factor 612
Kitchen Hygiene 613

ANNOTATIONS

Neomycin 615
Electron Sterilization 615
Medical Bibliography 616
Linear Accelerators 616

CORRESPONDENCE

The Difficulty in Medical Education. L. J. WITTS, M.D. 622
Training for General Practice. GEOFFREY EVANS, M.D.; H. R. E. WALLIS, M.D.; W. E. HAYES, B.M.; A. W. B. LOUDON, M.D.; W. A. BELLAMY, M.R.C.S.; G. W. DRYLAND, M.B.; D. HAMILTON, M.B. ..622
Psychology as Science. B. HART, M.D.; W. BROWN, D.M.; E. A. BENNET, M.D. 623
Inflammability of Ethyl Chloride. T. H. S. Burns, B.M.; H. E VICKERS, M.D. 625
An Interesting Advertisement. J. D. SUTHERLAND, M.B., and J. BOWLBY, M.D. 625

SUPPLEMENT

Health Service in Australia — PUBLIC HEALTH DISPUTE—INCREASES OF PAY IN ARMED FORCES—SCOTTISH CHEMISTS TO LEAVE HEALTH SERVICE—RECIPROCITY WITH CHANNEL ISLANDS 125
SIR CHARLES HASTINGS FESTIVAL 126

CORRESPONDENCE—*cont.*

Chlorinated Swimming Pools and Poliomyelitis. R. O. WARD, F.R.C.S. 625
The Internal Spermatic Fascia. D. W. BRACEY, F.R.C.S.Ed. 625
Domiciliary Treatment of Tuberculosis. B. MEYER, M.B.; WILLIAM D. GRAY, M.B.; S. S. CHATTERJEE, M.B. 626
The Case for Abortion. EUSTACE CHESSER, L.R.C.P.Ed. 626
Abortion. ANDREW M. CLAYE, F.R.C.O.G. 627
Haemorrhage from Peptic Ulcer. W. MICHIE, F.R.C.S.Ed.; D. J. R. STEEN, F.R.C.S. 628
Extreme Hyperpyrexia with Recovery. J. T. ROWLING, M.B. 628
Sulphonamide Therapy. J. L. BARFORD, M.R.C.S. 628
Poliomyelitis and Inoculations. L. RETI 628
But was it Poliomyelitis? FLORENCE M. E. DAVIES, M.B. 629
Treatment of Acute Yellow Atrophy. A. L. LATNER, M.D. 629
Osteoarthritis. F. V. STONHAM, F.R.C.S. 629
Penicillin and the Skin. E. F. BLUMBERG, M.D. 629
Strangulated Hernia in Infants. M. P. BROWNE, M.R.C.S. 629
Damage to the Antrum during Dental Extraction. W. O. LODGE, F.R.C.S.Ed. 630
Minority Crusade. LENNOX JOHNSTON, M.B., and F. C. MORGAN, M.R.C.S. 630
Johann Mikulicz-Radecki. S. GALEWSKI, M.D. 630

Epidemiology Section 634

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4679, WEEKLY, PRICE 2/-

Copyright

REGISTERED AS A NEWSPAPER

Emergency measure..

The anticipated effects of glucose as an energiser and restorer are to some extent lost if the patient shows a degree of unwillingness to accept it.

But the common aversion to the sickly, sometimes nauseating, taste of glucose in many of its ordinary forms is strikingly absent whenever LUCOZADE is offered.

LUCOZADE is so palatable, so refreshing, that neither children nor adults ever need urging to take it as prescribed.

(Containing Dextrose, Maltose and Dextrin in solution equivalent to 23% w/v Liquid Glucose B.P.)

LUCOZADE

An improved form of glucose therapy

LUCOZADE LTD., GT. WEST RD., BRENTFORD, MIDDX. M.16

Protein in Gastric Disturbances

PATHOLOGICAL lesions of the gastro-intestinal tract create special problems of management from the nutritional aspect. The problem is by no means eased by the fact that the body's protein requirements are increased rather than lessened by reason of the need for amino acids, which are required in the process of tissue repair. Failure to provide protein supplement in the diet can only mean that the body will have to obtain the required amino acids by raiding tissue proteins, which of course can only result in loss of weight.

The physician frequently has recourse to a non-residue diet in the management of gastric or duodenal ulcer and also in the re-establishment of a normal diet after infective enteritis or amœbic dysentery.

Difficulties of digestion, accompanied by pain, poor absorption and indifferent appetite, create a vicious circle which demands a special effort to break. This effort is sometimes provided by a protein supplement which can be easily broken down by the digestive processes and completely absorbed.

The particular advantages of Brand's Essence under such conditions are:—

1. It is soluble animal protein of high biological value.
2. Being partly hydrolysed, it is capable of easy ingestion, digestion and absorption.
3. It promotes gastric secretion.
4. It is extremely palatable.
5. It may be taken as a jelly or a liquid.

BRAND'S ESSENCE (OF MEAT)

When they're 'all legs'

Suddenly the children start to look like young colts, they get through one pair of shoes after another . . . .

This is the age — the pre-teens — when buying Clarks Shoes is a particularly sound investment, not merely because of the supple and enduring leather but because of their *fit* — plus the extra space at the toes.

Clarks footgauge decides which of the four-widths-to-each-size is the child's 'own.' A well-fitting Clarks shoe does not "scuff," it keeps its heel-shape—in short, like any tailored garment, it lasts. And—even more important—the child's feet stay straight and strong.

Clarks
SHOES
Established 1825

ZŌPLA

STRAPPING

Zōpla Strapping is a first class product for surgical use. Very strong cloths, the mass is powerfully adhesive. White and Flesh Cloths, also on Elastic Cloth.

WHITE FELT

Zōpla on White Felt is very popular for padding and protective purposes. Does not harden in use.

ZŌPLA-BAND

Zōpla-Band, Elastic Adhesive Bandage, ideal where elasticity is essential.

MANUFACTURED BY
LESLIES LTD
EST 1873
HIGHAM HILL RD
WALTHAMSTOW
LONDON, E.17

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 9 1950

STUDIES ON THE NATURE OF THE INTRINSIC FACTOR OF CASTLE*

BY

BYRON E. HALL, M.D.

Division of Medicine, Mayo Clinic, Rochester, Minnesota

In the years immediately following the demonstration by Minot and Murphy (1926) of the therapeutic efficacy of orally administered liver in pernicious anaemia, Castle and his associates (Castle, 1929; Castle and Townsend, 1929; Castle, Townsend, and Heath, 1930a; Castle, Heath, and Strauss, 1931; Castle and Ham, 1936; Castle, Heath, Strauss, and Heinle, 1937), in a series of brilliant investigations, concluded that there was in normal gastric juice from human beings a substance (intrinsic factor) which acted on a dietary substance (extrinsic factor) to produce a material required for the normal maturation of erythrocytes. Patients having pernicious anaemia lacked intrinsic factor.

Since these publications first appeared an intensive search has been made to isolate and to identify substances essential to haematopoiesis and to define the relationships between them. In recent years two pure compounds possessing marked haematopoietic activity have been obtained from liver. The first, pteroylglutamic acid, was isolated in 1943 (Pfiffner *et al.*, 1943) and synthesized in 1945 (Angier *et al.*, 1946). The second, vitamin B_{12}, was isolated in crystalline form in 1948 (Rickes *et al.*, 1948; Smith and Parker, 1948). Both substances possessed the property of converting megaloblastic erythropoiesis to a normoblastic type of regeneration, but only one, vitamin B_{12}, when administered parenterally, was found to be fully as effective as extracts of liver in controlling all manifestations of pernicious anaemia. Pteroylglutamic acid stimulated haematopoiesis, but failed to prevent the development or progression of the neurodegenerative changes characteristic of this disorder.

Vitamin B_{12}, therefore, appeared to be either the anti-pernicious-anaemia component of liver or a substance closely allied to it. However, in contrast to the haematopoietic activity of orally administered extracts of liver, vitamin B_{12}, in doses known to be effective parenterally, failed to produce a haematopoietic response when it was administered by mouth to patients having pernicious anaemia in relapse, unless gastric juice or other known sources of intrinsic factor were given simultaneously with it. Thus it appeared that vitamin B_{12} functioned also as extrinsic factor (Berk *et al.*, 1948; Hall *et al.*, 1949). Confirmation of the extrinsic-factor activity of this substance subsequently was obtained by the demonstration that it was an active haematopoietic component of beef muscle (Gardner *et al.*, 1949; Morgan *et al.*, 1949; Wolf *et al.*, 1950).

Since Minot and Castle (1931) had shown that liver extracts given by intramuscular injection were from thirty to sixty times as active as when administered by the oral route, it appeared to be advisable to determine the therapeutic activity of vitamin B_{12} administered orally in the absence of intrinsic factor, in doses in excess of those known to be effective parenterally. Few data are available in the literature concerning the minimal effective dose of orally administered vitamin B_{12}. In most instances only small quantities have been employed. However, Spies and his associates (1949) presented evidence to show that approximately fifty times the minimal effective parenteral dose is required when vitamin B_{12} is administered by mouth. On the other hand, Meyer and his associates (1950) observed no haematopoietic response to the daily oral administration of 150 μg. to one patient and of 250 μg. to a second patient. These quantities represent doses of from 150 to 250 times the minimal effective parenteral dose.

Oral Administration of Vitamin B_{12} in the Absence of Intrinsic-factor Activity

Nineteen patients having pernicious anaemia in relapse received vitamin B_{12} alone by mouth. Sixteen of the 19 were given the vitamin daily in doses varying from 5 to 100 μg. for periods of from seven to thirteen days (average ten days). The haematopoietic responses elicited are summarized in Table I.** Among 10 of 11 patients who ingested 5 to 10 μg. of vitamin B_{12} daily, haematopoietic

TABLE I.—*Oral Administration of Vitamin B_{12} in Absence of Intrinsic Factor to 19 Patients Having Pernicious Anaemia in Relapse*

Case	B_{12} Given Daily (μg.)	Days Observed	Erythrocytes (Millions per c.mm.)		Maximal Reticulocyte Response		
			Onset	End	% Observed	Day Observed	Expected*
1	5	7	1·52	1·63	4·9	2	22·3
2	5	12	2·64	2·05	3·5	1	7·5
3	5	10	1·89	1·27	—	—	15·6
4	5	9	2·50	2·84	2·3	9	8·4
5	5	10	2·53	2·81	—	—	8·4
6	5	9	2·40	2·02	2·7	5	9·4
7	10	9	1·64	1·95	—	—	20·4
8	10	13	2·32	2·74	6·1	10	10·5
9	10	9	2·30	2·36	3·6	2	10·5
10	10	9	2·39	2·31	—	—	9·4
11	10	9	2·08	1·90	—	—	12·9
12	25	11	2·63	3·43	5·2	12	7·5
13	25†	6	1·73	1·91	—	—	18·7
14	75†	7	1·47	1·50	8·0	5	22·3
	150†	9	1·50	1·60	4·9	9	22·3
15	1,000†‡	12	2·33	2·74	3·8	9	10·5
16	50	13	2·31	2·39	10·2	13	10·5
17§	100‡	13	1·65	2·10	7·1	6	20·4
18	100	8	2·01	2·29	5·7	7	14·1
19	100	10	1·35	2·17	13·0	8	26·5

* Sturgis † Single oral dose. ‡ Vitamin B_{12} concentrate. § Received one meal of cooked liver by error on second day of therapy.

*To be read at the First International Congress of Internal Medicine, Paris, September 11–14, 1950.

**Detailed data concerning the haematopoietic responses noted in these 19 patients have been published elsewhere.

responses either were not observed or they were of such minor degree that they were listed as being insignificant. One patient who received 10 μg. a day showed a significant although suboptimal response. Of the remaining five patients who received daily doses of vitamin B_{12} three were given 100 μg. daily, one 50 μg. daily, and one 25 μg. daily. It is of interest that the patient who ingested 25 μg. a day showed an optimal haematopoietic response, whereas two patients who received 100 μg. daily manifested distinctly suboptimal responses. The patient who was given 50 μg daily and one who was given 100 μg. a day had good but suboptimal responses.

Three of the 19 patients were given single oral doses of vitamin B_{12}, one receiving 25 μg., one 75 μg. on one occasion and 150 μg. seven days later, and one 1,000 μg. No haematopoietic response was observed in the patient ingesting 25 μg. of the vitamin, and the other two patients had suboptimal responses.

Studies on the Nature of Intrinsic Factor

Earlier studies on the nature of intrinsic factor in the gastric juice of human beings have demonstrated that the activity of the material is destroyed by heating to a temperature of 40° C. for three days, of 70° to 80° C. for thirty minutes, and by boiling for five minutes (Castle, Heath, and Strauss, 1931). Intrinsic factor may be separated from the enzymes pepsin and renin by precipitation with casein without losing its activity (Castle, Townsend, and Heath, 1930b ; Helmer *et al.*, 1934) and it is not destroyed by a degree of alkalinity (*p*H 9.8 for thirty minutes) which will inactivate pepsin and pepsinogen (Ungley and Moffett, 1936).

Intrinsic factor does not pass through a semi-permeable membrane which permits the passage of extrinsic factor. It is partially soluble in 80% alcohol and 80% acetone and is precipitated on saturation with ammonium sulphate (Helmer and Fouts, 1937 ; Goldhamer and Kyer, 1938).

The observations of Fouts, Helmer, and Zerfas (1935) on the intrinsic-factor activity of a powdered liver extract are of current interest in view of the isolation of vitamin B_{12} from liver. In 1935 these authors reported that the intrinsic factor contained in from 50 to 100 ml. of normal gastric juice seemed to be the minimal amount necessary to produce an optimal response when incubated with an extract derived from 100 g. of liver and administered by mouth daily to a patient with pernicious anaemia. Some response was obtained from as little as 10 ml. of the juice. The vitamin B_{12} content of the liver extracts employed in these studies is not known, but it seems probable that the daily dose supplied at least 10 μg.

In December, 1948, Berk and his associates demonstrated that vitamin B_{12} functions as food or extrinsic factor when administered by mouth simultaneously with gastric or intrinsic factor to patients having pernicious anaemia in relapse. Normal gastric juice from human beings was used as a source of intrinsic factor. They confirmed the observation of Castle and Ham (1936) that a haematopoietic response was not elicited if an interval of twelve hours elapsed between administrations of sources of extrinsic and intrinsic factors.

The findings of Berk and associates (1948) were confirmed by my associates and me (Hall *et al.*, 1949) in February, 1949. Berkefeld-filtered pooled gastric juice obtained from patients who had either duodenal ulcer or functional disturbances of the gastro-intestinal tract was employed. The haematopoietic activity of the simultaneous oral administration of 5 to 10 μg. of vitamin B_{12} and 100 to 150 ml. of Berkefeld-filtered pooled gastric juice of human beings is shown in Table II.

TABLE II.—*Oral Administration of Vitamin B_{12} and Pooled Filtered Gastric Juice of Human Beings*

Case	Period	Daily Oral Therapy		Days Observed	Erythrocytes (Millions per c.mm.)		Maximal Reticulocyte Response	
		B_{12} (μg.)	Source of Intrinsic Factor		Onset	End	%	Day
20	1	—	150 ml. of gastric juice	6	1·43	1·50	—	—
	2	5	,, ,,	18	1·50	2·92	31·7	10
21	1	5	,, ,,	12	1·63	2·40	16·5	9
15	1	1,000*	—	12	2·33	2·74	3·8	9
	2	10	100 ml. of gastric juice	11	2·74	2·71	11·8	7

* Single dose of vitamin B_{12} concentrate.

Since, as has previously been shown by others, intrinsic factor passes readily through a Berkefeld filter, the risk of the transmission of bacterial infections, such as tuberculosis, may be avoided when pooled gastric juice is administered to patients. It also makes possible the collection of relatively large quantities of gastric juice of normal or high acidity in the routine gastric laboratory for the purpose of studying the effects of various physical and chemical agents on intrinsic factor. A preliminary survey of the results of some of these studies has been reported (Campbell *et al.*, 1949).

Some of the earlier observations on the properties of intrinsic factor, derived either from gastric juice of human beings or from the stomach and intestines of swine, have been confirmed in our studies on the effectiveness of orally administered vitamin B_{12} when given in conjunction with various derivatives of gastric juice or gastro-intestinal substances to patients having pernicious anaemia in relapse.

Gastric juice heated to a temperature of 63° C. for thirty minutes was ineffective as an intrinsic factor when given to a patient with pernicious anaemia in a daily dose of 150 ml. together with 5 μg. of vitamin B_{12}. The patient subsequently responded well to 75 ml. of unheated gastric juice daily, with 5 μg. of vitamin B_{12} (Case 2, Table III).

TABLE III.—*Oral Administration of Vitamin B_{12} and Pooled Filtered Gastric Juice of Human Beings: Effect of Heat on Intrinsic Factor*

Case	Period	Daily Oral Therapy*		Days Observed	Erythrocytes (Millions per c.mm.)		Maximal Reticulocyte Response	
		B_{12} (μg.)	Intrinsic Factor		Onset	End	%	Day
2	1	5	150 ml. of gastric juice previously heated to 63° C. for 30 min.	12	2·64	2·05	—	—
	2	5	75 ml. of unheated gastric juice	13	2·05	3·38	11·3	11
3	1	Mixture of 5μg. of B_{12} + 100 ml. of gastric juice stored at 25° C. for 24 hours, then heated to 70° for 1 hour		10	1·89	1·27	—	—
	2	Unheated mixture of 5 μg. of B_{12} + 100 ml. of gastric juice stored at 25° C. for 24 hours		14	1·27	1·91	5·2	14
	3	Single intramuscular injection of 20 μg. of B_{12}. Same dose repeated 3 and 5 days later		8	1·91	2·64	—	—

* Unless otherwise specified.

Since a temperature of 63° C. is required to destroy most viruses, the administration of pooled gastric juice of human beings which possesses intrinsic-factor activity could result in the transmission of a virus infection, such as infectious hepatitis.

Vitamin B_{12}, unlike intrinsic factor, is not destroyed by relatively high temperatures. A thermostable combination of intrinsic factor and vitamin B_{12} was not obtained by allowing a mixture of the vitamin and neutralized gastric juice to stand for twenty-four hours at a temperature of 25° C. before heating to 70° C. for one hour. Such a mixture, containing 100 ml. of gastric juice and 5 μg. of vitamin B_{12}, administered daily to a patient having pernicious anaemia in relapse failed to produce a therapeutic response. During a second period an unheated mixture of the two substances after standing for twenty-four hours at 25° C. was administered orally each day. While the reticulocytosis was suboptimal, there was a significant rise in the erythrocyte count, and the subsequent administration of vitamin B_{12} intramuscularly did not elicit a second reticulocyte response (Case 3, Table III). It was concluded, therefore, that either vitamin B_{12} and intrinsic factor present in human gastric juice did not combine chemically, or if chemical union did occur the product of the interaction was also thermolabile.

Pooled Berkefeld-filtered gastric juice from human beings, collected and stored for three months at a *p*H of 1.7 and a temperature of 5° C., retained intrinsic-factor activity although it appeared to be less active than the fresh material. The results of the daily oral administration of 5 μg. of vitamin B_{12} and 100 ml. of stored gastric juice to two patients having pernicious anaemia in relapse are shown in Table IV. One patient (Case 22, period 2)

TABLE IV.—*Oral Administration of Vitamin B_{12} and Pooled Filtered Human Gastric Juice: Presence of Intrinsic Factor After Storage for Three Months at pH 1.7 and 5° C.*

Case	Period	Daily Oral Therapy*		Days Observed	Erythrocytes (Millions per c.mm.)		Maximal Reticulocyte Response	
		B_{12} (μg.)	Intrinsic Factor		Onset	End	%	Day
22	1	—	100 ml. of fresh gastric juice	10	2·91	2·78	5·8	2
	2	5	100 ml. of gastric juice stored 3 months at *p*H 1·7 and 5° C., then neutralized to *p*H 7	11	2·78	2·66	7·0	10
	3	5	100 ml. of fresh gastric juice	6	2·66	3·18	6·3	6
23	1	—	100 ml. of fresh gastric juice	7	1·25	1·31	3·3	7
	2	5	100 ml. of gastric juice stored 3 months at *p*H 1·7 and 5° C., then neutralized to *p*H 7	12	1·31	2·20	13·5	7
	3	10 μg. of B_{12} administered intramuscularly daily for 5 days, then weekly		21	2·31	3·56	—	—

* Unless otherwise specified.

manifested a reticulocyte peak equal to the estimated maximal response calculated for the initial level of erythrocytes, but there was no rise in the erythrocyte count during administration of the mixture. Since secondary reticulocytosis was demonstrated during period 3, when the patient received vitamin B_{12} and fresh gastric juice, the haematopoietic response to the oral administration of the vitamin and the stored gastric juice probably was suboptimal. The other patient (Case 23), on the other hand, showed a significant haematopoietic response that approached an optimal figure.

At low temperatures the enzymic action of pepsin is largely inhibited, and previously reported observations by Castle and Ham have indicated that loss of the intrinsic-factor activity of gastric juice on standing may be due to inactivation by the native pepsin contained in the juice.

A 95% solution of ethyl alcohol apparently destroys intrinsic factor, inasmuch as no significant haematopoietic activity could be demonstrated in either the precipitate or the soluble fraction of gastric juice when these fractions were administered with vitamin B_{12} successively to a patient having pernicious anaemia in relapse (Case 24, Table V).

TABLE V.—*Oral Administration of Vitamin B_{12} and Precipitates of Gastric Juice of Human Beings*

Case	Period	Daily Oral Therapy		Days Observed	Erythrocytes (Millions per c.mm.)		Maximal Reticulocyte Response	
		B_{12} (μg.)	Intrinsic Factor		Onset	End	%	Day
24	1	5	Cold alcohol precipitate derived from 150 ml. of gastric juice	10	2·44	2·22	4·5	7
	2	5	Alcohol-soluble fraction derived from 150 ml. of gastric juice	9	2·22	2·10	5·7	5
	3	5	75 ml. of gastric juice	11	2·10	2·87	9·8	8

In November, 1949, Ternberg and Eakin reported that normal gastric juice contained a heat-labile non-dialysable substance which combined with vitamin B_{12} in such a manner as to make the vitamin unavailable for the growth of certain bacteria (*Bacterium coli, Lactobacillus lactis* Dorner, *Lactobacillus leichmannii*). The application of heat to the complex thus formed liberated vitamin B_{12}, whereupon the vitamin again became available for microbial growth. Heated gastric juice did not contain a principle capable of combining with vitamin B_{12}. Ternberg and Eakin (1949) postulated that the heat-labile factor in gastric juice, which they called "apoerythein," either was intrinsic factor itself or an important component of this factor. Commercial preparations of gastric mucosa of swine made for therapeutic use were found to contain a principle which seemed to be analogous to the apoerythein in gastric juice.

Subsequently, Eakin (unpublished data) reported that apoerythein possessed all of the known chemical properties of intrinsic factor. Its concentration was found to be greater in the gastric juice of normal subjects than in that of patients having pernicious anaemia. Eakin estimated that 25 μg. of vitamin B_{12} could be bound by the apoerythein contained in 1.5 litres of gastric juice. This amount of juice is an approximation of the volume secreted by a normal person in twenty-four hours. Apoerythein was found in the lining of the gastro-intestinal tract of all vertebrates studied. Its presence was not demonstrable in other tissues.

In a collaborative study with Dr. Frank Bethell and his associates of the University of Michigan, my associates and I (unpublished data) reported recently the enhancement of haematopoietic activity of orally administered vitamin B_{12} when preparations of stomach and duodenum of swine were given with the vitamin. The results of the simultaneous administration of vitamin B_{12} and extracts of gastric mucosa of swine to two patients with pernicious anaemia in relapse are shown in Table VI. The lyophilized preparation had greater activity than the non-lyophilized material. However, of the extracts employed by us, greatest intrinsic-factor activity was found in the lyophilized non-dialysable fraction of a dilute hydrochloric acid extract of duodenal mucosa. A dilute acid extract of ground whole duodenum, prepared at a *p*H of 3 to 4, was found to be moderately effective when given daily in a dose of 2 g. of desiccated material together with 5 μg. of vitamin B_{12}. Desiccated duodenal mucosa without extraction or fractionation also possessed considerable therapeutic

TABLE VI.—*Oral Administration of Vitamin B_{12} and Extracts of Gastric Mucosa of Swine*

Case	Period	Daily Oral Therapy*		Days Observed	Erythrocytes (Millions per c.mm.)		Maximal Reticulocyte Response	
		Time	Material Given		Onset	End	%	Day
25	1	10 p.m.	5·4 g. of non-lyophilized extract of hog gastric mucosa	7	2·01	1·89	3·9	3
	2	10 p.m.	5 μg. of B_{12} + 5·4 g. of non-lyophilized extract of hog gastric mucosa	13	1·89	1·30	7·2	11
	3	10 p.m.	5 μg. of B_{12} + 75 ml. of pooled human gastric juice	11	1·30	1·32	8·6	5
	4		5 μg. of B_{12} intramuscularly	9	1·32	2·57	20·5	4
26	1	10 a.m. 10 p.m.	10 μg. of B_{12} 4 g. of lyophilized extract of hog gastric mucosa	9	1·64	1·95	—	—
	2	10 p.m.	10 μg. of B_{12} + 4 g. of lyophilized extract of hog gastric mucosa	15	1·95	2·04	11·3	10
	3		5 μg. of B_{12} intramuscularly	7	2·04	2·37	—	—

* Unless otherwise specified.

activity when administered by mouth in a dose of 2 to 4 g. together with 5 μg. of vitamin B_{12}.

Bethell and his associates have assayed the vitamin-B_{12}-binding power of these materials and of the gastric juice of normal human beings, according to the method of Ternberg and Eakin, employing the test organism *Lactobacillus leichmannii*. The materials, after sterilization by passage through a Berkefeld filter without heating, were added to the culture medium. The highest binding activity of the duodenal materials tested was shown by the water-soluble non-dialysable fraction of duodenal mucosa. The acid extract of ground whole duodenum possessed about half and the desiccated unfractionated duodenal mucosa about an eighth of the activity of the water-soluble non-dialysable material.

The property of binding vitamin B_{12} shown by derivatives of the lining of the gastro-intestinal tract, which inhibits the characteristic stimulation of microbial growth exerted by the vitamin, should serve as a useful adjunct to the concentration and purification of intrinsic factor. Nevertheless, it seems probable that natural substances other than intrinsic factor may possess the property of combining with vitamin B_{12} in a similar manner. Thus

TABLE VII.—*Oral Administration of Vitamin B_{12} and Egg-white Lysozyme*

Case	Period	Daily Oral Therapy*		Days Observed	Erythrocytes (Millions per c.mm.)		Maximal Reticulocyte Response	
		B_{12} (μg.)			Onset	End	%	Day
7	1†	10	100 mg. of egg-white lysozyme	13	2·32	2·74	6·1	10
	2	10	" "	14	2·74	2·61	3·0	8
	3	Complex formed by 10 μg B_{12} + 200 mg. of egg-white lysozyme		11	2·61	2·71	—	—
	4	10	2·1 g. extract of hog duodenum	11	2·71	3·03	4·0	7
	5	10	150 ml. of gastric juice	11	3·03	3·68	—	—
	6	10 μg. of B_{12} intramuscularly		7	3·77	3·92	—	—
12	1	25		11	2·63	3·43	5·2	12
	2	Complex formed by 25 μg. of B_{12} + 500 mg. of egg-white lysozyme		16	3·43	3·27	—	—

* Unless otherwise specified.
† Vitamin B_{12} and egg-white lysozyme administered separately at an interval of twelve hours each day.

C. E. Meyer and his associates (1950) reported that lysozyme derived from egg white formed a complex with vitamin B_{12} which prevented stimulation of the growth of the test organism *Lactobacillus lactis* Dorner by the vitamin. Therapeutic trials on two patients with pernicious anaemia in relapse, employing daily oral doses of a complex of egg lysozyme and amounts of vitamin B_{12} up to 25 μg., have indicated that lysozyme has no significant potentiating effect on orally administered vitamin B_{12}. The results of these observations are shown in Table VII. Recently, two extracts of the gastric mucosa of swine, which showed a strong binding capacity for vitamin B_{12}, as determined by the Ternberg–Eakin method, were found to possess little or no intrinsic-factor activity when tested clinically on patients with pernicious anaemia in relapse (Table VIII).

TABLE VIII.—*Oral Administration of Vitamin B_{12} and Extracts of the Gastric Mucosa of Swine: Poor Haematopoietic Response from Extracts Showing a Strong Binding Capacity for the Vitamin*

Case	Period	Daily Oral Therapy*		Days Observed	Erythrocytes (Millions per c.mm.)		Maximal Reticulocyte Response	
		Time	Medication		Onset	End	%	Day
9	1	10 a.m. 10 p.m.	10 μg. of B_{12} + 0·5 g. of gastric mucosa of swine	9	2·30	2·36	3·6	2
	2	10 p.m.	10 μg. of B_{12} + 0·5 g. of extract of gastric mucosa of swine	10	2·36	2·86	3·4	8
	3	10 p.m.	10 μg. of B_{12} + 1 g. of extract of gastric mucosa of swine	8	2·86	3·22	—	—
	4	10 p.m.	10 μg. of B_{12} + 150 ml. of pooled gastric juice of human beings	9	3·22	3·20	3·3	9
	5		10 μg. of B_{12} intramuscularly for 6 days	9	3·20	3·68	—	—
27	1	9 p.m.	5 μg. of B_{12}	9	2·40	2·55	2·7	5
	2	9 p.m.	5 μg. of B_{12} + 1·2 g. of extract of gastric mucosa of swine	11	2·55	3·00	2·0	4

* Medication administered orally unless otherwise specified.

Comment

Vitamin B_{12}, administered parenterally, is as effective as extracts of liver in the treatment of pernicious anaemia. However, when it is administered by mouth the presence of a potentiating agent is required for its effective utilization. In the absence of such an agent the haematopoietic responses to the oral administration of vitamin B_{12}, in doses up to 100 times the minimal effective parenteral dose, are variable and unpredictable.

Potentiation may be provided by known sources of intrinsic factor, such as the gastric juice of human beings and extracts of the stomach and intestines of swine. Extracts of stomach or duodenum of swine possess intrinsic-factor activity, the activity in duodenal mucosa of swine appearing to be greater than that contained in the entire wall of the stomach or duodenum. However, concentrated preparations that yield consistently effective and reliable therapeutic results when given in relatively small doses have not yet been produced. The barrier to the manufacture of dependable commercial products of this nature has been the destruction of a portion or all of the activity of the intrinsic factor during the process of concentrating gastric or duodenal substances. Until methods for preserving intrinsic-factor activity have been devised, patients with pernicious anaemia who are receiving preparations containing vitamin B_{12} by the oral route must be observed closely, and parenteral therapy substituted if the

haematopoietic and clinical response to oral therapy is not satisfactory.

It would appear that the solution to effective oral therapy is dependent on a clearer understanding of the factors governing absorption in the gastro-intestinal tract. The demonstration by Ternberg and Eakin that vitamin B_{12} may be "bound" by a substance or substances in normal gastric juice of human beings and in the lining of the gastro-intestinal tract of vertebrates, thereby rendering the vitamin no longer available for the growth of certain bacteria, is important, even though present evidence suggests that this method cannot be used solely as an *in vitro* test for intrinsic-factor activity.

The assumption seems warranted that the role of intrinsic factor must be concerned with absorption of vitamin B_{12} by (1) altering the chemical or physical nature of the compound so that it more readily traverses the intestinal barrier; (2) protecting the vitamin from destruction by secretions of the digestive tract; or (3) preventing the removal of the vitamin from the contents of the upper part of the gastro-intestinal tract by micro-organisms. Little direct evidence has been brought forward in support of any of these hypotheses.

With respect to the possible removal of vitamin B_{12} by bacteria within the gastro-intestinal tract of patients with pernicious anaemia it is pertinent to recall some conclusions to which Davidson (1928) was led by his studies on the gastro-intestinal flora in pernicious anaemia. In 1928 Davidson stated: "A great numerical increase of organisms, normal inhabitants of the bowel—e.g., *Bact. coli*, streptococci, and especially *Cl. welchii*—was found in the gastro-intestinal contents of cases of pernicious anaemia. . . . The great quantitative increase of bacteria, especially at levels of the small intestine which in normal persons are relatively bacteria-free, may be a factor of great aetiological importance." Dick (1941) reported his finding of the almost constant presence of bacteria of the colon and lactis-aerogenes group in the fasting gastric contents of patients with pernicious anaemia, and suggested that there was a profound derangement of the whole gastro-intestinal tract in persons with this disease, which permitted the return of colon bacilli from the colon to the stomach. Recently Davis and Mingoli (personal communication) have shown that *Bact. coli* have an avidity for vitamin B_{12}, and Lichtman, Ginsbert, and Watson (unpublished data) have reported that the daily oral administration of 3 g. of "aureomycin" and 3 μg. of vitamin B_{12} to patients having pernicious anaemia in relapse is followed by haematopoietic responses. Since aureomycin would be expected to reduce greatly the number of coliform organisms in the gastro-intestinal tract, vitamin B_{12} may thereby be made more available for absorption. Studies along this line would appear to be a promising field of investigation.

Summary and Conclusions

In pernicious anaemia, orally administered vitamin B_{12} requires for its effective utilization the presence of a potentiating agent (intrinsic factor of Castle). In the absence of this factor the haematopoietic responses obtained from the oral administration of the vitamin, in doses up to 100 times the minimal effective parenteral dose, are variable and unpredictable. Potentiation may be provided by known sources of intrinsic factor, such as gastric juice of normal or elevated acidity from human beings and extracts of the stomach and intestines of swine. Concentrated preparations that yield consistently effective and reliable therapeutic results, however, have not yet been produced, owing to the ready destructibility of intrinsic factor and the consequent loss of a portion or all of the intrinsic-factor activity during the process of concentrating gastric or duodenal substances. It is believed that the studies herein reported support the concept of the enzymic nature of intrinsic factor.

References

Angier, R. B., Boothe, J. H., Hutchings, B. L., Mowat, J. H., Semb, Joseph, Stokstad, E. L. R., SubbaRow, Y., Waller, C. W., Cosulich, Donna, Fahrenbach, M. J., Hultquist, M. E., Kuh, Erwin, Northey, E. H., Seeger, Doris R., Sickels, J. P., and Smith, J. M., jun. (1946). *Science*, **103**, 667.
Berk, Lionel, Castle, W. B., Welch, A. D., Heinle, R. W., Anker, Rudolf, and Epstein, Martin (1948). *New Engl. J. Med.*, **239**, 911.
Campbell, D. C., Hall, B. E., and Morgan, E. H. (1949). *J. Lab. clin. Med.*, **34**, 1590.
Castle, W. B. (1929). *Amer. J. med. Sci.*, **178**, 748.
—— and Ham, T. H. (1936). *J. Amer. med. Ass.*, **107**, 1456.
—— Heath, C. W., and Strauss, M. B. (1931). *Amer. J. med. Sci.*, **182**, 741.
—— —— —— and Heinle, R. W. (1937). Ibid., **194**, 618.
—— and Townsend, W. C. (1929). Ibid., **178**, 764.
—— —— and Heath, C. W. (1930a). Ibid., **180**, 305.
—— —— —— (1930b). *J. clin. Invest.*, **9**, 2.
Davidson, L. S. P. (1928). *J. Path. Bact.*, **31**, 557.
Davis, B., and Mingoli, E. S. Personal communication.
Dick, G. F. (1941). *Amer. J. digest. Dis.*, **8**, 255.
Eakin, R. E. Unpublished data.
Fouts, P. J., Helmer, O. M., and Zerfas, L. G. (1935). *Ann. intern. Med.*, **8**, 790.
Gardner, F. H., Harris, J. W., Schilling, R. F., and Castle, W. B. (1949). *J. Lab. clin. Med.*, **34**, 1502.
Goldhamer, S. M., and Kyer, Jean (1938). *Proc. Soc. exp. Biol., N.Y.*, **37**, 659.
Hall, B. E., Bethell, F. H., Cintron-Rivera, A. A., Miller, S., Campbell, D. C., and Morgan, E. H. Unpublished data.
—— Morgan, E. H., and Campbell, D. C. (1949). *Proc. Mayo Clin.*, **24**, 99.
Helmer, O. M., and Fouts, P. J. (1937). *Amer. J. med. Sci.*, **194**, 399.
—— —— and Zerfas, L. G. (1934). Ibid., **188**, 184.
Lichtman, H., Ginsbert, V., and Watson, J. Unpublished data.
Meyer, C. E., Eppstein, S. H., Bethell, F. H., and Hall, B. E. (1950). *Fed. Proc.*, **9**, 205.
Meyer, L. M., Sawitsky, Arthur, Cohen, B. S., Krim, Mendel, Fadem, Robert, and Ritz, N. D. (1950). *Bull. N.Y. Acad. Med.*, **26**, 263.
Minot, G. R., and Castle, W. B. (1931). *Ann. intern. Med.*, **5**, 159.
—— and Murphy, W. P. (1926). *J. Amer. med. Ass.*, **87**, 470.
Morgan, E. H., Hall, B. E., Campbell, D. C. (1949). *Proc. Mayo Clin.*, **24**, 594.
Pfiffner, J. J., Binkley, S. B., Bloom, E. S., Brown, R. A., Bird, O. D., Emmett, A. D., Hogan, A. G., and O'Dell, B. L. (1943). *Science*, **97**, 404.
Rickes, E. L., Brink, N. G., Koniuszy, F. R., Wood, T. R., and Folkers, Karl (1948). Ibid., **107**, 396.
Smith, E. L., and Parker, L. F. J. (1948). *Biochem. J.*, **43**, viii.
Spies, T. O., Stone, R. E., Lopez, G. G., Milanes, Fernando, Toca, R. L., and Aramburu, T. (1949). *Lancet*, **2**, 454.
Ternberg, J. L., and Eakin, R. E. (1949). *J. Amer. chem. Soc.*, **71**, 3858.
Ungley, C. C., and Moffett, Robert (1936). *Lancet*, **1**, 1232.
Wolf, D. E., Wood, T. R., Valiant, John, and Folkers, Karl (1950). *Proc. Soc. exp. Biol., N.Y.*, **73**, 15.

The World Health Organization reports a striking reduction in the malaria rate among the rural population of the Mymensingh District of East Bengal (Pakistan), where a W.H.O. malaria control demonstration team for the past year has been carrying out residual spraying operations with D.D.T. Dr. G. Gramiccia (Italy), the leader of the team, states that not a single case of new infection has been detected in people living in the area which has been covered since this time last year in the spraying operations. There has been a reduction in the rate of enlarged spleen from 74.5% to 21.2% of the children of the area. Incidence of malaria parasites in the blood has been reduced from 22% in May, 1949, to 1.3% in May, 1950. Meanwhile, in the surrounding unsprayed areas the percentages of enlarged spleen and malaria parasites in the blood of children tested have been increasing. In 1949 protection against malaria was provided by this team's operations to about 35,000 people. More than 22,500 separate rooms were sprayed. Dr. Gramiccia added that these encouraging results have had a profound effect on the population, who had taken a rather diffident and sometimes openly hostile attitude at the first. Now they not only are appreciative but earnestly request the continuation of the spraying and the extension of the programme to neighbouring regions.

CORTISONE (COMPOUND E)

SUMMARY OF ITS CLINICAL USES*

BY

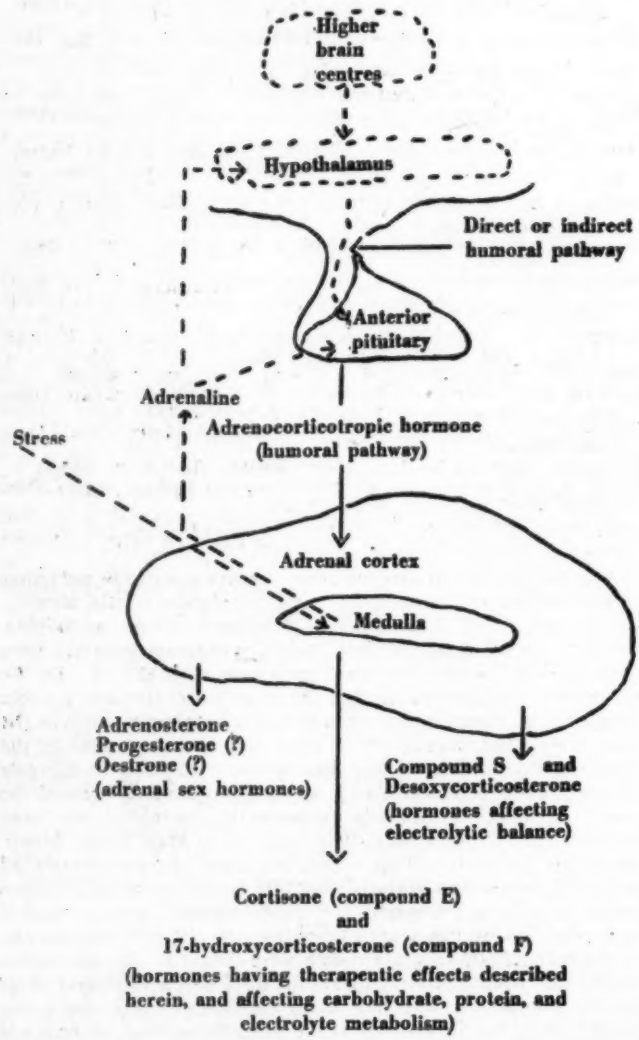
J. M. CARLISLE, M.D.

Medical Director, Merck and Co., Inc., Rahway, N.J., U.S.A.

Cortisone is one of the series of crystalline hormonal substances isolated from extracts of the adrenal cortex in the laboratory of Dr. E. C. Kendall, of the Mayo Foundation. This substance, originally named "compound E," was isolated from beef adrenal glands and described by Mason, Myers, and Kendall in 1936. It was also described independently by Reichstein as "substance FA," and by Wintersteiner and Pfiffner as "compound F."

Cortisone was first synthesized from a bile acid in 1946 by Dr. L. H. Sarett, of the Research Laboratories of Merck and Co., Inc. The availability of cortisone in sufficient quantities for clinical use was the result of a practical synthesis developed by the combined efforts of Dr. Kendall and his associates and of Dr. Max Tishler and his associates in the Merck Research Laboratories.

PITUITARY—ADRENAL RELATIONSHIPS



*A paper to be read at the First International Congress of Internal Medicine, Paris, September 11–14, 1950.

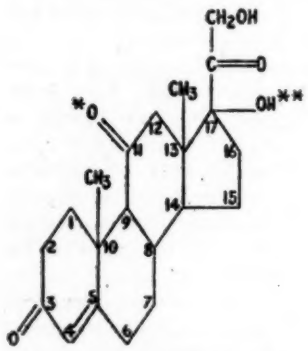
Theoretic Mechanism of Adrenal Secretion of Cortisone and Related Adrenal Steroids

The adrenal cortex upon stimulation elaborates (1) the group of hormones producing the therapeutic effects described herein and affecting carbohydrate, protein, and electrolyte metabolism, such as cortisone and compound F; (2) the group affecting electrolyte balance, such as compound S and desoxycorticosterone; and (3) the adrenal sex hormone adrenosterone, and possibly progesterone and oestrone. The present concept is that the secretion of cortical steroid hormones is mainly or entirely mediated through stimulation of the adrenal cortex by the adrenocorticotropic hormone of the anterior pituitary (see Diagram).

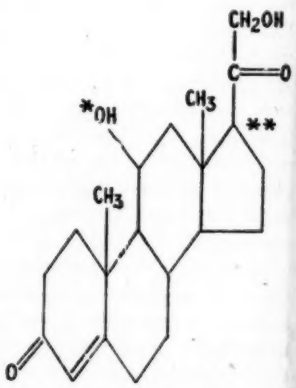
Specificity of the Chemical Structure of Cortisone

From the formula below it will be seen that cortisone has an oxygen atom at position 11* and a hydroxyl group (OH) at position 17**, and that these features differentiate it structurally from the earlier-named corticosterone.

Although the presence of an oxygen atom at position 11 and a hydroxyl group at position 17 are features which are vital to the biological activity of cortisone (and which have required much attention in the synthesis of the hormone),



Cortisone (Kendall's compound E). The chemical name, 17 - hydroxy - 11-dehydrocorticosterone, is based upon points of difference and similarity between the molecular structures of cortisone and corticosterone (Kendall's compound B).



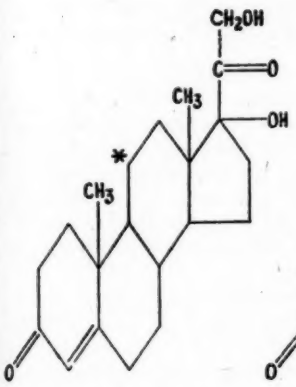
Corticosterone (Kendall's compound B)

it should also be noted that every other atom and configuration of the molecule probably is equally important. This is indicated by the fact that dozens of similar steroids have been prepared and tested for the antirheumatic and other therapeutic activity of cortisone, and that none possesses such activity (with the probable exception of compound F), although chemically each may differ very slightly from cortisone. Examples of a few of these "analogues" are given on the opposite page.

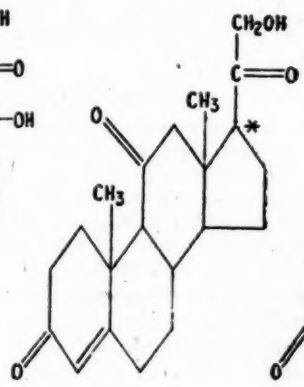
The list could be extended to include many more compounds, now numbering almost fifty, which have been synthesized and tested for cortisone-like activity. As each has been tested and negative results obtained, the remarkable specificity of the cortisone molecule has again been emphasized.

Metabolic Effects

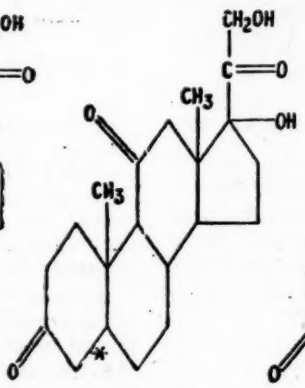
Electrolyte balance is affected in varying degrees in different cases. Retention of sodium and water early in the course of treatment is often observed, especially when high dosage of cortisone has been employed, but is usually followed by spontaneous diuresis on continued



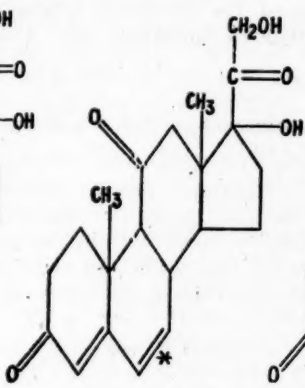
Reichstein's compound S (11-desoxy-17-hydroxycorticosterone, or "desoxycortisone"). *Molecule differs from cortisone only by the absence of an oxygen atom at position 11.



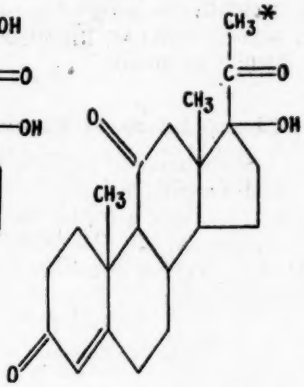
Kendall's compound A (11-dehydrocorticosterone). *Molecule differs from cortisone only by the absence of a hydroxyl group at position 17.



Dihydrocortisone. *Molecule differs from cortisone only by absence of a double bond at position 4, 5 (presence of an extra hydrogen atom).



6, 7 - Dehydrocortisone. *Molecule differs from cortisone only by presence of a double bond at position 6, 7 (absence of a hydrogen atom).



21 - Desoxycortisone. *Molecule differs from cortisone only by the absence of an oxygen atom at position 21.

administration of the hormone or after its discontinuation. In several instances, however, sodium and water retention has been so great as to require lowering the dosage or discontinuing administration of the drug because congestive heart failure with ascites or peripheral or pulmonary oedema developed. Sodium retention can be diminished or avoided by the restriction of sodium intake alone, or together with the use of diuretics during administration of the drug. High dosage of cortisone has caused increased urinary excretion of potassium, with metabolic alkalosis in some cases. In these patients potassium depletion resulting from such loss has produced symptoms of weakness, electrocardiographic changes characteristic of hypopotassaemia (such as lowering of T waves, and depression of the S-T segment and S-T junction), and hypotension. This development can be avoided by carefully following the CO_2-combining power, E.C.G., and chloride depletion. If any changes indicating alkalosis are noted, the dosage of cortisone should be reduced, or potassium administered concomitantly with the hormone. Also, it should be noted that in such cases the use of diuretics may provoke a further dangerous diuresis of potassium.

Carbohydrate metabolism may be affected also, in that blood-sugar levels may be increased and the response to insulin decreased. In patients with diabetes mellitus, insulin requirements are increased during administration of the hormone, but revert to their original levels soon after discontinuation of the drug.

Protein metabolism is affected in many patients, especially those receiving high dosage of cortisone. The continued administration of large doses usually produces a negative nitrogen balance, which may be overcome in certain instances by increased food intake. Where reversed albumin–globulin ratios are present, these tend to revert towards normal. Creatinuria is increased, uric acid excretion increased, and changes in the pattern of amino-acid excretion occur.

Studies in animals suggest that cortisone may inhibit the growth of granulation and fibrous tissues. Clinical studies also have provided evidence which suggests that the hormone may retard wound healing. This must be further evaluated, but these data should be considered when surgical procedures are contemplated in patients receiving cortisone, especially patients with ulcerated or inflamed lesions and those who show evidence of hypoproteinaemia, hypovitaminosis, and general malnutrition.

General Physiological or Hormonal Effects

Cortisone is a potent hormonal substance, and definite physiological effects are to be expected from its administration. With high or prolonged dosage, and in certain patients on the recommended dosage, undesired hormonal effects may occur. However, as with other hormones, such effects are reversible and disappear after administration of the substance is discontinued.

In some patients the drug has produced such evidences of hyperadrenalism as rounding of the face, mild hirsutism, acne, striae of the skin, and, in a few instances, amenorrhoea. All these phenomena disappeared after administration was discontinued.

In animal investigations, prolonged administration of large doses of cortisone may cause reduction in the size of the adrenal cortex. In man, muscular weakness and asthenia have been reported for brief periods after treatment was abruptly withdrawn. This suggests that a transient period of adrenal cortical insufficiency may exist when administration of the drug is stopped. In certain patients a temporary reduction of urinary corticoids and 17-ketosteroids is found; a temporary hypoglycaemia and suppression of eosinophil response occasionally occur.

Electroencephalogram.—In several patients an increase of approximately 10% in the frequency of alpha waves has been observed. This finding is said to indicate increased cerebral activity.

Other Physiological Effects

Cortisone has rarely caused a significant increase of blood pressure, but this possibility exists where sodium and water retention occurs. The resting blood pressure in patients with essential hypertension may be decreased. In some cases decrease in prothrombin time has been noted.

Certain mental effects have been reported. Definite improvement in the mental attitude of patients receiving this drug usually occurs, often with acceleration of the alpha waves of the electroencephalogram. In certain instances the increase in psychomotor activity has temporarily produced an exaggerated sense of well-being and, infrequently, a manic state. Conversely, mental depression has been reported in a few cases. Insomnia has been noted in some individuals. In rare instances pre-existent or latent mental derangement, such as schizophrenia, seems to have been intensified or precipitated. In such cases

premonitory symptoms of the psychotic reaction usually occur, such as pronounced insomnia and exaggerated swings of mood.

Clinical Effects in Rheumatoid Arthritis and its Variants

In rheumatoid arthritis and its variants, such as rheumatoid spondylitis (Marie–Strümpell disease), Still's disease, and psoriatic arthritis, the usual pattern of response is, first, diminution in subjective stiffness, usually within 24 to 48 hours, but sometimes within six hours after the initial dose (Table I) : in many cases this symptom is significantly

TABLE I.—*Response of Various Diseases to Cortisone*

Beneficial Effect Often Dramatic	Results Encouraging But Require Further Evaluation	Transient Beneficial Effects Observed	No Beneficial Effects Established
Rheumatoid arthritis	Various allergies: Hay-fever Angioneurotic oedema Drug sensitization Serum sickness	Acute leukaemia (lymphocytic or granulocytic)	Diabetes mellitus (increases insulin requirement)
Rheumatic fever		Multiple myeloma	Myasthenia gravis
Rheumatoid spondylitis		Lymphosarcoma	Cushing's syndrome
Still's disease	Acute gouty arthritis	Hodgkin's disease	Amyotrophic lateral sclerosis
Psoriatic arthritis	Ulcerative colitis	Chronic lymphatic leukaemia	Multiple sclerosis
Lupus erythematosus (early)	Regional enteritis		Progressive muscular dystrophy
Addison's disease	Nephrotic syndrome		Progressive muscular atrophy
Asthma (status asthmaticus)	Scleroderma (early)		Congestive heart failure (may be detrimental in some cases, but cases secondary to acute carditis may be benefited through effect of cortisone on inflammatory lesions)
	Dermatomyositis		
Inflammatory eye diseases	Psoriasis		
Exfoliative dermatitis	Periarteritis nodosa (early)		Chronic myelogenous leukaemia
Pemphigus	Pulmonary granulomatosis		Acute monocytic leukaemia
Panhypopituitarism	Alcoholism (?)		Glomerulonephritis (exclusive of nephrotic syndrome)
			Poliomyelitis
			Osteoporosis (may be detrimental?

or completely relieved within a few days. Next, articular tenderness and pain on motion decrease. Finally, swellings of the joints diminish, sometimes fairly rapidly and completely, but occasionally more slowly and incompletely. In many patients mild soft-tissue deformities of the knees or elbows have disappeared within seven to ten days. An increase in muscle strength has been reported. The extent of return to normal has been limited, as must be expected, by the degree of permanent pathological change present.

The appetite usually improves rapidly, and many patients have described a loss of the feeling of malaise associated with the disease and have experienced a sense of well-being, occasionally within several hours after initial administration of the drug.

When cortisone is discontinued signs and symptoms may begin to reappear within 24 to 48 hours, becoming gradually worse during the following two to four weeks. The degree of relapse varies, and is apparently unrelated to the duration of treatment. In some individuals, however, the greater part of the remission of signs and symptoms achieved after use of the drug has persisted for as long as several weeks or months. If the drug is readministered when manifestations of the disease return, prompt remission is again induced.

Laboratory Findings

Erythrocyte Sedimentation Rate.—Elevated sedimentation rates are decreased, sometimes rapidly, during the administration of cortisone, usually becoming normal within 10 to 35 days. Occasionally, however, the rate does not return to normal, but is definitely reduced. In a few instances, persistently high sedimentation rates may be lowered by temporarily increasing the daily dose of the drug.

Haemoglobin.—Low haemoglobin values tend to increase when cortisone is administered. Increases of 2 g. within several weeks have been observed.

Erythrocytes.—Increases of as much as 1,000,000 red cells per c.mm. of blood have been observed in anaemic patients during cortisone therapy of two weeks' duration or longer.

Serum Protein.—Increased serum-globulin levels and low or reversed albumin–globulin ratios usually return towards normal, in most cases promptly, during treatment, but gradually revert to pretreatment levels when the drug is discontinued.

Arterial Synovial Biopsy.—Findings after several weeks of cortisone therapy included almost complete disappearance of lymphocytic reaction, improvement in appearance of collagen, and the presence of many fibroblasts in more adult form. Though not normal, the synoviae revealed definite evidence of healing.

17-Ketosteroids.—During administration of cortisone, urinary 17-ketosteroid values are initially reduced, but they usually rise again, and to a somewhat higher level. When large doses (e.g., 200 mg. daily) are employed the ketosteroids may remain slightly above the pretreatment level throughout the period of administration.

Corticosteroids.—The urinary concentrations of corticosteroids are initially increased by administration of cortisone and may reach a peak of excretion of about 5 mg. per 24 hours soon after treatment is started. The amount excreted then declines gradually to a fairly constant level, ranging from 1 to 2 mg. per 24 hours, on continued administration of the drug. On discontinuing cortisone therapy following prolonged treatment periods or after the injection of large doses of the drug, both 17-ketosteroid and corticosteroid excretion has been observed to diminish temporarily in certain patients.

Clinical Effects in Acute Rheumatic Fever

Within 24 hours after the initial injection of cortisone patients have usually described a sense of well-being and appeared alert instead of ill and "toxic." Temperatures that had been elevated usually became normal within one to four and a half days. Appetites have usually improved, with resultant gains, reaching 5 to 12 lb. (2.3 to 5.4 kg.) in 18 to 28 days in some cases.

Painful, swollen, and inflamed joints have in most instances become symptom-free after three and a half to six days of treatment with cortisone. In most of the patients with acute rheumatic fever improvement has been maintained for periods of three months or longer following treatment. Several patients with acute rheumatic fever who relapsed after the drug was discontinued responded promptly to another series of injections, and have remained apparently well since discontinuation of the drug a second time. While cortisone has demonstrated its value in curtailing the acute manifestations of rheumatic fever, long-term studies will be necessary to evaluate its effects on the development of cardiac lesions.

Effects on Cardiovascular System

Pulse Rate.—Tachycardia, when present, disappeared in three and a half to five days after treatment was started. Bradycardia, ranging from 44 to 60 beats a minute, accompanied the use of the drug in some cases. The bradycardia persisted while

the young adult patients were receiving 200 mg. a day of cortisone, but disappeared shortly after the dose was reduced to 100 mg. daily.

Blood Pressure.—Significant blood-pressure changes have been observed infrequently during or following treatment of acute rheumatic fever with cortisone.

Electrocardiographic Findings.—In patients with prolonged P-R intervals return to normal or nearly normal limits usually occurred within eight days after the beginning of treatment. Electrocardiograms, made daily, showed no evidence of toxic effects on the heart.

Laboratory Findings

Erythrocyte Sedimentation Rate.—Usually the elevated sedimentation rate became normal within 12 to 18 days after injection of cortisone was begun.

Haemoglobin.—Increase in haemoglobin value by as much as 2.4 g. occurred within three weeks in patients in whom the pretreatment levels were low.

Leucocyte Count.—No characteristic effect on the total number of circulating leucocytes was noted during administration of cortisone, despite rapid clinical improvement and reduction of the erythrocyte sedimentation rate.

Serum Proteins.—In almost every instance administration of cortisone caused a slight increase in the values for serum albumin and a reduction in the values for serum globulin.

Response in Other Diseases

Disseminated Lupus Erythematosus.—Cortisone has produced a temporary beneficial effect in most cases in which treatment was started in the early stages of the disease. Elevated temperatures and sedimentation rates have been lowered, joint symptoms improved, and the skin lesions in certain cases alleviated. The general condition of the patient also has been improved. These effects generally last from a few days to a few weeks, and even longer in some patients. Favourable response cannot be expected in late cases with advanced renal involvement, azotaemia, hypoproteinaemia, retinal haemorrhages, and cachexia. Because of the frequent involvement of the heart and kidneys in this disease, the physician should be particularly watchful for evidence of aggravation of salt and water retention and congestive heart failure in response to cortisone.

Bronchial Asthma.—Cortisone administered to patients in status asthmaticus has in most instances produced relief of the symptoms, and in certain patients has increased the vital capacity. The improved state has lasted from several weeks to several months in many of the cases.

Non-specific Iritis, Iridocyclitis, Uveitis, and Sympathetic Ophthalmia.—Striking improvement during the course of cortisone administration has been reported. Congestion has decreased and vision has improved to some extent. In some cases these benefits occur rapidly, but further investigation is necessary before any conclusions can be drawn concerning the efficacy of cortisone in the treatment of these conditions. Recent reports indicate that local ophthalmic instillation of cortisone (as a 1:4 dilution of the standard formulation in physiological saline solution) may also be effective. (Such instillation should be made at intervals of 30 to 60 minutes throughout the waking hours.)

Skin Conditions.—Cortisone has been tried in a variety of severe skin conditions, including pemphigus, angioneurotic oedema, atopic dermatitis, and exfoliative dermatitis, including cases secondary to drug reactions. In general, its use has resulted in improvement, with rapid subsidence of the inflammatory reaction.

Addison's Disease.—Cortisone has been highly effective in controlling Addison's disease, in conjunction with D.C.A. (desoxycorticosterone acetate) and/or supplementary sodium chloride (for special dosage see below).

Leukaemias and Lymphomas.—In some cases of acute leukaemia, especially in children, there is a temporary response to treatment with cortisone, but relapses are to be expected. Even in those cases in which there is an initial response, refractoriness to cortisone develops during repeated courses of the substance. Chronic lymphatic leukaemia, lymphosarcoma, and Hodgkin's disease also have shown transient involution of neoplastic masses. The peripheral blood picture of chronic lymphatic leukaemia apparently is not altered appreciably. Acute monocytic leukaemia and chronic myeloid leukaemia have shown no response to cortisone therapy in several cases treated.

Other Conditions.—Cortisone has been used in investigations of several other conditions, but the data are still very incomplete and inconclusive. From the information available at present, it appears that cortisone does not produce any significant benefit in chronic gout, myasthenia gravis, amyotrophic lateral sclerosis, or congestive heart failure. It has no appreciable effect on the late structural changes of the rheumatic diseases.

Dosage

With high or prolonged dosage, and in certain patients on the recommended dosage (see below), undesired hormonal effects may occur. The physician planning to use cortisone should have received instruction in its use and should familiarize himself with the published literature before attempting treatment.

The treatment should be given only to patients in hospitals which have adequate facilities operated by trained technicians and under the supervision of a qualified physician. Facilities should be available for electrocardiography and for routine blood determinations, such as blood sugar, carbon-dioxide-combining power, and, where possible, for blood electrolytes. Facilities for laboratory studies must be available during the entire course of treatment.

Although cortisone has now been used in over 3,000 individual cases, the duration of clinical study has been less than two years and only a small number of cases have been observed over this entire period. In no instance has continuous treatment been used for a longer period than eight months. Therefore it must be realized that recommendations are limited by the extent of this experience, and that optimal-dosage schedules are still tentative. The administration of cortisone must be carefully adjusted for each patient and regulated according to the effects observed. Failure to obtain an expected therapeutic response suggests, in the absence of any undesirable effects, the possible need for a temporary increase in dosage.

Dosage in Rheumatoid Arthritis

Initial Dosage.—When a maximal response to cortisone is desired in rheumatoid arthritis in adults, the following schedule is strongly recommended: 100 mg. every eight hours for three doses, then 100 mg. every 12 hours for two doses, followed by 100 mg. every 24 hours for 7 to 14 days (the last can be given as a single injection or as a divided dose of 50 mg. every 12 hours. In some cases it seems that the single injection is better). In all cases the injections should be made deeply into the gluteal muscles, at the outer upper quadrant of the buttock. The optimal dosage for children has not been established, but it seems to be more nearly proportional to the severity of the disease than to body size. A comparatively large dose, or the adult dose, may be necessary and is often well tolerated.

Subsequent Dosage.—When the desired response appears to have been obtained the dosage should be lowered gradually in a stepwise manner. The total daily dose should be reduced by 10 or 15 mg. at two- to three-day intervals until the total daily dose is 50 mg. The schedule may then be changed to 100 mg. every other day (or 100 mg. on Monday and Wednesday, and 100 or 200 mg. on Friday). If at any time during the change-over significant relapse occurs, 100 mg.-a-day dosage must be reverted to until the desired response again appears, before lowering the dosage.

Temporary Increases in Dosage.—If the expected response is not obtained within four to five days after initiating cortisone therapy according to the schedule suggested above, the dosage should be increased to 100 mg. every 12 hours for four doses and then again reduced to 100 mg. daily. If inadequate dosage is employed it is likely that the desired beneficial effect will not be obtained. It is essential for many patients that a temporary increase in dosage, as outlined above, be given in order to provide the greatest relief.

Rest Period.—A rest period of not less than three or four weeks should be allowed between courses of treatment with cortisone in order to permit recovery of adrenal activity. A " course " at full therapeutic dosage is generally considered to extend over a period of two to six weeks, and the total dosage per course should not exceed 3 to 4 g.

Dosage in Rheumatic Fever

Optimal dosage for treatment of rheumatic fever has not been established. In the adult cases treated thus far, 200 mg. of cortisone was injected intramuscularly daily for 10 to 19 days, and, following this, 100 mg. daily for 5 to 27 days.

It is suggested that, as a general practice, courses of treatment be extended over a period of 10 to 14 days, with rest periods of varying duration between the courses (see under " Dosage in Rheumatoid Arthritis "), but it is more important that the natural history of the disease be taken into account and that re-treatment be instituted as indicated by recurrence of signs and symptoms of reactivation of the disease, such as return of fever, increase of sedimentation rate, recurrence of arthralgia, and lengthening of the P-R interval.

Dosage in Other Diseases

For eye and skin conditions and the leukaemias and lymphomas the required dosage seems to be comparable to that outlined for rheumatoid arthritis. Somewhat larger doses may be required initially in bronchial asthma, but the duration of treatment necessary is usually not more than five to ten days. In Addison's disease 25 mg. daily, or less, may be adequate, but supplementary salt or desoxycorticosterone should be given concurrently, as indicated, to maintain normal values of blood electrolytes.

Special Precautions

It must be emphasized most strongly that cortisone is an agent with powerful biological actions. The patient receiving cortisone must be closely watched at all times for the development of unfavourable side-reactions. The most important precautions relative to these are :

1. *Evaluation of Relative Contraindications Before Using Cortisone.*—As in the case of other powerful therapeutic agents having potentially harmful effects, the physician must weigh the advantages of treatment with cortisone against the possible deleterious effects. This consideration is crucial where relative contraindications exist, such as diminished cardiac reserve or congestive heart failure, latent or overt psychotic tendencies, diabetes mellitus, and the debility accompanying advanced cachectic states, uraemia, and senescence.

2. *Restriction of Dietary Sodium Chloride.*—Salt and water retention is a common occurrence after several days of full cortisone dosage. Usually there is a gain of only a few pounds in weight and minimal dependent oedema. This may progress, however, and result in pronounced oedema, including pulmonary oedema, or cardiac enlargement and congestive failure, especially in patients with previously diminished cardiac reserve. Occasionally such symptoms may come on quite suddenly. There may be some elevation of arterial blood pressure. Measurement of fluid intake and output and daily weighing of the patient provide the best indices of fluid retention. When salt and fluid retention occurs the simplest treatment is the low-sodium diet. If sodium intake is kept below 1 g. daily for a few days it is usually possible to prevent or correct fluid retention. In some instances it may be necessary to decrease cortisone dosage or even discontinue it.

3. *Correction of Hypopotassaemia.*—When hypopotassaemia develops, supplementary administration of potassium chloride may be required. It is important to note carefully the discussion under " Metabolic Effects," relative to hypochloraemic-hypopotassaemic metabolic alkalosis.

4. *Control of Hyperglycaemia.*—When a patient with diabetes mellitus is treated for a concurrent disease amenable to cortisone the diabetic status must be followed and regulated with great care. It is usually possible to compensate for the anti-insulin effect of cortisone by administering larger doses of insulin—double the usual requirement may be needed. In treating non-diabetic individuals the physician should be aware of the possibility that cortisone may induce renal glycosuria or hyperglycaemia with glycosuria. In all such cases thus far reported these changes have disappeared soon after cortisone administration was discontinued.

5. *Detection of Early Psychic Disturbances.*—Although the usual psychic reaction to cortisone is a desirable increase in the sense of well-being, an occasional individual will develop pronounced psychic derangements, especially where high dosage has been used for protracted periods, but sometimes early during the course of therapy. These reactions include a wide array of phenomena ranging from pronounced euphoria to frank psychoses. Therefore, treatment should be continued with caution when early signs of such reactions appear. The premonitory symptoms are marked swings of mood, severe insomnia, bad dreams, and increased psychomotor activity.

6. *Supervision of Patient Following Cortisone Therapy.*—After discontinuation of cortisone supervision is essential, for this substance may continue to act for some time after the last injection, or there may be a sudden reappearance of severe manifestations of the disease for which the patient was treated. In a few cases following prolonged high dosage, evidence of a temporary hypo-adrenal state may be observed if treatment is withdrawn abruptly. Weakness and hypoglycaemia may occur, but return of adrenal function may be expected within two weeks.

Theories of the Mechanism of Action of Cortisone

It may be said at the outset that the fundamental nature of the action of cortisone against disease processes is unknown. During the past eighteen months, however, much valuable and intensive work has been directed towards the solution of this problem—a widespread

TABLE II.—*Certain Known (or Probable) Effects of Cortisone*

Metabolic	Interendocrine	Neuromuscular	Immunological and Serological	Cytological	Enzymological
Increases gluconeogenesis	May either depress thyroid activity (probably via diminished pituitary production of thyrotropic hormone) or increase sensitivity of tissues peripherally to thyroid hormone	Restores capacity of muscle for work in adrenalectomized animals	Tends to bring about a restoration of normal A.-G. ratio in disease	Produces lymphopenia (some species) and eosinopenia in peripheral blood	Diminishes hyaluronidase activity
Lowers renal threshold for glucose	Increases insulin requirement. In individuals with normal pancreatic reserve this requirement is adequately met, but in latent or overt diabetes additional insulin must be administered	May cause increased activity in electroencephalogram (increase in frequency of alpha waves) or appearance of abnormal slow rhythms	Diminishes antibody response to typhoid antigen in rabbits	May increase tissue eosinophils and metaplasia of fibroblasts into eosinophils	Probably reduces blood glutathione
Opposes the action of insulin	Relative hypoglycaemia may occur after withdrawal of cortisone	May restore electroencephalographic pattern to normal in Addison's disease	Diminishes or abolishes tuberculin reaction	Inhibits fibroplasia	May be involved in enzyme systems concerned with pigmentation of skin
Increases mobilization and utilization of fat	Restores normal diuretic response to ingested water in Addison's disease	May induce euphoria and increased psychomotor activity	May prevent vascular lesions otherwise resulting from injection of D.C.A. (rats) or heterologous serum (rabbits)	Increases growth of macrophages in tissue culture	Increases arginase in liver and kidney of mice
Increases protein catabolism, urinary nitrogen, and urinary uric acid	May delay or inhibit menstruation, probably via depression of pituitary gonadotropic activity	May precipitate psychotic reaction (probably only in predisposed individuals)	Prevents or reduces tissue reaction to chemical irritants (guinea-pigs)	Stimulates reticulocyte production or release	Increases urinary excretion of uropepsin in patients with Addison's disease
Increases deposition of hepatic glycogen		May increase muscle strength (in rheumatoid arthritis) or may cause muscle weakness (probably only in cases of hypopotassaemia)	May inhibit formation of histamine	May bring about polycythaemia	
May bring about retention of sodium				May increase neutrophils in peripheral blood	
Increases urinary excretion of chloride and potassium				Causes involution of lymphoid tissue and of certain neoplastic tissues	
May increase calcium and phosphorus excretion					

research effort which may be expected to bring about a new concept of the nature of disease itself.

It seems likely that cortisone does not act therapeutically through a single circumscribed mechanism, but that this action must involve the many known physiological properties of the hormone as well as various undiscovered effects of this substance on the chemical processes of organs, tissues, and cells of the normal and the diseased organism. At the present time we have information indicating that (1) cortisone and/or compound F is involved in the metabolism of carbohydrate, protein, and fat; (2) it is necessary to the normal function of certain endocrine organs; (3) it exerts profound effects on neuromuscular metabolism; (4) it has distinct immunological effects; (5) it can bring about remarkable cytological changes; and (6) it is involved in several specific enzyme systems (see Table II).

It is for future research to determine which of these effects, or others, are fundamentally associated with the therapeutic activity of cortisone, and which ones are associated only coincidentally. The tendency to oversimplify the problem must be avoided, since it is clear that the hormone is implicated, directly or indirectly, in a large number of the physiochemical processes of the vertebrate organism.

Looking Ahead

The body of knowledge concerning the exact value of cortisone in the treatment of the variety of diseases discussed above is rapidly growing, as is the understanding of its pharmaco-physiological effects. Steadily increasing supplies of cortisone are becoming available; so that clinical and experimental studies are rapidly expanding in number and scope. So, too, the periods of observation on patients already treated are lengthening, and the results are becoming more measurable. Combined, these factors assure that a more exact appraisal of the effects of cortisone will shortly be possible.

A technical committee of the British Standards Institution has devised simple common names for certain pest-control products. A list of 25 names is being circulated for comment among Government departments, manufacturers, and scientific societies before final publication. In order to pre-empt the use of these names as proprietary names, the list has been lodged with, and approved by, H.M. Patent Office.

STREPTOMYCIN AND NEOMYCIN*

AN ANTIBIOTIC APPROACH TO TUBERCULOSIS

BY

SELMAN A. WAKSMAN, Ph.D.

(*From the Department of Microbiology, Rutgers University, New Brunswick, N.J., U.S.A.*)

"This attempt to place between the covers of a book the record of a drug discovered less than five years ago is a daring and unprecedented one. It suggests a wealth of knowledge, established despite the haste of its gathering. It is particularly daring in the instance of tuberculosis, a disease so chronic in its habit that phthisiologists rarely do more than describe its victims as 'apparently' cured, and so multiple in its manifestations that it required the discovery of the tubercle bacillus to unify its many forms beneath a single name."—Walker, Hinshaw, and Barnwell (Waksman, 1949).

Historical

The history of tuberculosis is as old as that of man himself. It was, however, the discovery of the causative agent of this disease, *Mycobacterium tuberculosis*, by Robert Koch that stimulated the search for "cures" of this "white plague" of man. Most of these, ranging from the tuberculin of Koch himself to the much publicized "gold cure" of recent years, led to serious disappointments. The antibiotics, or those compounds of microbial origin that have the capacity of inhibiting and even of destroying in very dilute solutions the growth of other microbes, especially the causative agents of disease, have given new hope for a final solution of this ancient disease. Although most of the antibiotics are not very effective against the acid-fast bacteria, a few have proved to be highly effective against the mycobacteria, including the tuberculosis organism. Side by side with the discovery of antimycobacterial agents of microbial origin, progress has also been made in the use of synthetic compounds which are non-toxic but still active enough to justify their use in chemotherapy.

*A paper to be read at the First International Congress of Internal Medicine, Paris, September 11–14, 1950

The utilization of micro-organisms as well as their products for the treatment of tuberculosis is not of recent origin. The first attempt at such treatment was made soon after the tuberculosis organism was isolated. Cantani tried in 1885 to utilize living saprophytic bacteria for combating tuberculosis; he was soon followed by Babes, who in 1888 used bacterial products. Later, Rappin and Vaudremer, in 1912–13, treated many patients with products of bacterial metabolism and with metabolic products and cell constituents of fungi, respectively. In general, the history of bacteriotherapy of tuberculosis is a long one (Waksman, 1947). Numerous investigators established beyond question that various saprophytic and pathogenic micro-organisms have the capacity to inhibit the growth of and even to destroy the *M. tuberculosis*. Further studies brought out the fact that this is due primarily to certain well-defined chemical compounds which these micro-organisms are able to produce when grown in artificial culture media and which are now known as antibiotics.

It has been definitely established that the ability to form antibiotics which are active upon the *M. tuberculosis* is widely distributed among various groups of micro-organisms. At least 16 products of fungi, 11 bacterial preparations, and 10 antibiotics of actinomycetes have been isolated and are now well recognized. They are listed in Table I. Most of these compounds or preparations proved

TABLE I.—*Production by Different Micro-organisms of Antibiotics Possessing Antituberculosis Properties*

Fungi	Actinomycetes	Bacteria
Aspergillic acid	Actinomycin	Ayfivin
Aspergillin	Anti-smegmatis factor	Bacillin
Biformin	Litmocidin	Endosubtilisin
Clitocybine	Mycomycin	Esperin
Diploicin	Neomycin	Eumycin
Enniatin	Nocardin	Gramicidin
Gliotoxin	Streptin	Licheniformin
Helvolic acid (fumigacin)	Streptothricin	Micrococcin
Javanicin	Streptomycin	Nisin
Lactaroviolin	Mannosidostreptomycin	Pyolypic acid
Lateritiin		Subtilin
Mycocidin		
Nebularin		
Polyporin		
Usnic acid		
Ustin		

to be, for one reason or another, quite unsuitable as chemotherapeutic agents. Some were too toxic, others were inactive or insufficiently active in the animal body. Some of them, however, gave definite promise of becoming important tools in combating tuberculosis. Most important of these proved to be streptomycin, an antibiotic produced by an actinomyces, *Streptomyces griseus*, which has already found extensive application in the therapy of tuberculosis.

Antimycobacterial Properties of Streptomycin

Streptomycin is highly active against various strains of *M. tuberculosis* (Waksman, 1949). The degree of sensitivity varies considerably, however, as shown in Table II. Of particular importance is the fact that upon contact with streptomycin, or upon continued administration of this

TABLE II.—*Comparative Effects of Neomycin and Streptomycin Upon the Growth of Different Mycobacteria (Waksman et al., 1949). Growth Inhibition in Units (for Neomycin) or in Micrograms (for Streptomycin) Per Millilitre of Broth After 14 Days' Incubation*

Organism	Neomycin	Streptomycin
M. avium	0·1–0·3	10·0
M. tuberculosis H37Rv	0·2–1·0	1·0–5·0
M. tuberculosis H37RvR*	0·2–1·0	5,000
Mycobacterium 607	0·1	0·2–0·4
Mycobacterium 607R*	0·25	300

*R = Streptomycin-resistant strain.

drug to diseased persons, some of the strains tend to develop resistance to the antibiotic. This is shown in Table III, in which the sensitivity of different freshly

TABLE III.—*Comparative Effects of Streptomycin and Neomycin Upon Freshly Isolated Strains of M. tuberculosis (Waksman et al., 1949)*

Strain No.	Source of Culture	Amount of Antibiotic Required to Inhibit Growth in Liquid Medium	
		Streptomycin	Neomycin
		μg./ml.	units/ml.
100	Sinus left hip	1 to 5	<0·5
500	Sinus left flank	1 to 5	<0·5
575	Bladder	>100	<0·5
910	Gastric	1 to 5	<0·5
209	Sputum	1 to 5	<0·5
684	Urine	>100	<0·5

isolated strains of the pathogen to streptomycin, as compared with neomycin, is presented.

As is shown below, the search for a second antibiotic was stimulated by this limitation of streptomycin—namely, the rapidity with which bacteria develop resistance to it. Both the streptomycin-sensitive and streptomycin-resistant strains of different mycobacteria are sensitive to neomycin. This is true of saprophytic and pathogenic forms, whether the resistance is natural or is acquired by contact with streptomycin.

Search for New Agents

The discovery of streptomycin, and its extensive application in the treatment of various forms of tuberculosis, has aroused great interest on the part of bacteriologists, chemists, and clinicians, and has resulted in further extensive searches for new substances, microbial or synthetic in origin, which would overcome the limitations of streptomycin.

In the search for and selection of new antimicrobial agents, four postulates may be made (Waksman *et al.*, 1949):

1. These substances must be active, not only *in vitro* but also *in vivo*, against the specific micro-organisms. It is desirable that this activity be greater than that of other substances which are now recognized as useful or promising.

2. They must be active against those strains of the disease-producing micro-organisms which are not sensitive or which have become resistant to other chemotherapeutic agents.

3. They should not favour the development of resistance among sensitive bacteria; at least, the new agents should permit lesser emergence of such resistance than existing agents.

4. They should be of low toxicity to animals, or at least they should be no more toxic than agents now used in chemotherapy.

Many organisms have been tested for their capacity to produce such antibiotic agents. Various substances have been isolated in our laboratory since the isolation of streptomycin was reported in 1944, and their activity *in vitro* and *in vivo* has been determined. Of these, only one, neomycin, was found to satisfy the postulates. This conclusion was reached after extensive comparative studies of the effect of streptomycin and neomycin upon various bacteria. These included test-tube studies of both saprophytic and pathogenic mycobacteria and animal studies of both antibiotics against various Gram-positive and Gram-negative bacteria. These studies brought out the following facts:

1. Neomycin is more active than streptomycin against both the saprophytic *Mycobacterium* 607 and the human and animal pathogenic strains of *M. tuberculosis*.

2. Neomycin is as active against the streptomycin-resistant strains of the above organisms as against the sensitive ones.

3. Neomycin favours to a far less degree than does streptomycin the development of resistant strains of mycobacteria; it is true that on prolonged serial transfer of large numbers of cells a considerable increase in resistance may be obtained, but the rate of increase is much slower than in the case of streptomycin.

4. Neomycin is characterized by a relatively low toxicity in animals and has a high therapeutic index.

Before examining the limited experimental and clinical data now available for neomycin, it may be of interest to summarize briefly the very extensive literature on the effect of streptomycin upon tuberculosis. For a detailed review reference can be made to the various works dealing with this subject (Fanconi and Löffler, 1948; Florey *et al.*, 1949; Riggins and Hinshaw, 1949; Waksman, 1949).

Effect of Streptomycin in Experimental and Clinical Tuberculosis

In the first studies on the treatment of experimental tuberculous infections in guinea-pigs with streptomycin the results obtained were strikingly better than those previously reported with the use of various other chemotherapeutic agents. This is brought out in Fig. 1. Feldman and Hinshaw were soon able to state emphatically: "The evidence obtained from the many studies of the effect of streptomycin on the natural course of experimental tuberculosis in animals amply justifies the conclusion that this antibiotic is a highly potent antagonistic agent for tuberculous infections in animals produced by fully virulent tubercle bacilli of human or of bovine type."

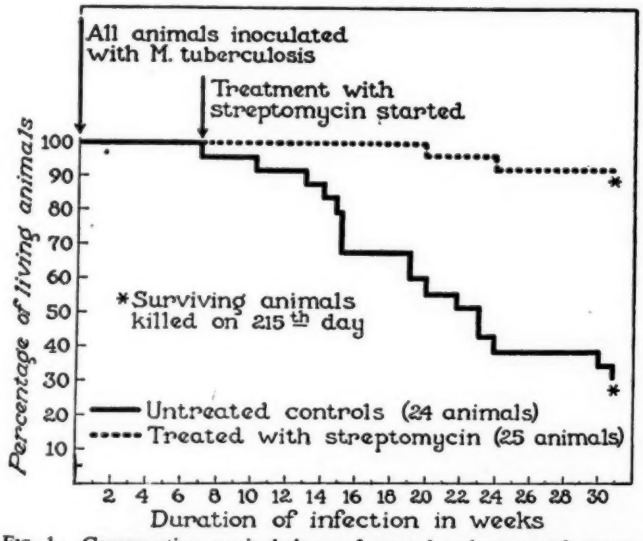


FIG. 1.—Comparative survival times of treated and untreated groups of guinea-pigs (from Feldman, Hinshaw, and Mann, 1945).

Clinical investigations soon followed (Hinshaw and Feldman, 1945; Hinshaw *et al.*, 1946a, 1946b). The first results obtained with streptomycin proved to be encouraging. It is now barely five years since the first clinical cases were reported and since the first attempt was made to manufacture streptomycin in sufficient amounts for large-scale clinical evaluation; a wealth of information which permits certain broad generalizations has already accumulated.

In general, the laboratory demonstrations of the effectiveness of streptomycin *in vitro*, followed by the experimental proof of its usefulness in experimental animals, were fully substantiated by numerous clinical investigations. The large-scale studies conducted in England by the Medical Research Council (1948), and in the United States by the Veterans Administration (Council on Pharmacy and Chemistry, 1950) and the American Trudeau Society (1950), produced adequate evidence that an agent for the treatment of tuberculosis was finally available. Although many hundreds of drugs were previously reported to control the tubercle bacillus in the culture tube, none were able to do so in the animal body. Many drugs that have been effective against the infection in animals were found to be impracticable against the same disease in man. In the case of streptomycin the analogy from laboratory to animal to man held well. It was only in the clinic, however, that investigators finally learned of the potentialities of streptomycin, on the one hand, and of its limitations and dangers on the other.

The clinical usefulness of streptomycin has been carefully summarized by Riggins and Hinshaw (1949) and by Walker, Hinshaw, and Barnwell (Waksman, 1949).

In submitting its report to the Council on Pharmacy and Chemistry (1950), the committee in charge of the work at the Veterans Administration emphasized the importance of combining surgical procedures with chemotherapy. The use of daily doses of 1 g. or less has decidedly reduced the incidence of toxic manifestations. The development of resistant micro-organisms was delayed, especially by the combined administration with para-aminosalicylic acid.

The American Trudeau Society Committee (1950) recommended for adults 1 g. of streptomycin, administered in a single dose intramuscularly, or 1 or 2 g. of dihydrostreptomycin in one or two injections. In miliary tuberculosis and tuberculous meningitis in adults, 2 or 3 g. a day, given intramuscularly in two or three doses of 1 g. each, was recommended. To overcome the emergence of streptomycin-resistant organisms, it has been recommended that streptomycin be administered at greater intervals, as 1 g. every third day or twice a week, or that its daily administration be combined with para-aminosalicylic acid.

It may be of interest to consider in somewhat greater detail certain special forms of tuberculosis.

Meningeal and Acute Miliary Tuberculosis

Since they were first recognized, these two types of tuberculosis have involved a mortality rate of 100%. The time between onset of disease and death was measured in weeks, especially in meningitis. These two forms provided, therefore, an ideal testing ground for the efficacy of streptomycin. It has fully justified itself. Its ability to suppress or destroy the tubercle bacillus was demonstrated. The effectiveness of streptomycin is now generally agreed on by investigators in the U.S.A., in England, and in other European countries. In one series of 100 patients with proved diagnoses, 24 were alive between 14 and 26 months after treatment had been instituted. These results are given in Table IV.

TABLE IV.—*Effect of Streptomycin on Acute Miliary and Meningeal Tuberculosis (From Walker, Hinshaw, and Barnwell—Waksman, 1949)*

Nature of Disease	No. of Patients	No. Living*	No. Dead After Start of Treatment in Months			
			0–1·5	1·5–6	>6	Total
Acute miliary ..	19	12	3	2	2	7
Meningeal	43	9	16	11	7	34
Miliary and meningeal	25	2	14	6	3	23
Meningeal developing during or after treatment for miliary ..	13	1	3	4	5	12
Total ..	100	24	36	23	17	76

* All patients still living 14 to 26 months after start of treatment.

Pulmonary Tuberculosis

Pulmonary tuberculosis is commonly considered, both in incidence and in the number of lives it takes, as one of the most serious forms. Since 1900 the mortality rate of tuberculosis has been reduced in the U.S.A. to 20% of its previous rate. In 1942, however, 52,000 deaths were still ascribed to tuberculosis, and of these 92% were due to pulmonary disease. The situation is worse in many European and Asiatic countries, particularly since the recent war. The prolongation of life in patients with meningeal and miliary tuberculosis was ample evidence that streptomycin had a definite effect on tuberculosis. The chronic nature of pulmonary tuberculosis suggests that years will pass before the effectiveness of streptomycin can be evaluated by its effect on the mortality rate.

In the relatively short period since its introduction, however, there has been substantial agreement among investigators that certain immediate results may be expected from its use. The question of toxicity and the development of bacterial resistance were the two controlling factors in establishing the most desirable duration of treatment. Originally a period of 120 days was selected. To lessen the incidence of resistance a decrease in duration of treatment has often been recommended. A reduction in efficacy did not seem to accompany a reduction in duration of treatment to 60 days. A further reduction to 42 days appeared to decrease the efficacy of streptomycin but certainly did not destroy it. The tendency over the last two years has been to reduce the daily dosage of streptomycin from 2 g. to 1 g. or even to 0.5 g. and to reduce the period of treatment from 120 days to 60 days or even less. The first is an attempt to avoid toxicity, and the second to reduce the incidence of resistance.

In a comprehensive study of the effectiveness of streptomycin in tuberculosis carried out under the auspices of the British Medical Research Council (1948), the conclusion was reached that the course of bilateral acute progressive disease can be halted by streptomycin therapy :

"Fifty-one per cent. of the streptomycin-treated patients showed considerable improvement radiologically when comparison was made with their chest radiographs taken on admission. That streptomycin was the agent responsible for this result is attested by the presence in this trial of the control group of patients, among whom considerable improvement was noted in only four (8%), and two of these four patients had improved only after collapse therapy. In other words, streptomycin therapy was effecting what the patient's tissues alone could not do—checking the spread of the tubercle bacillus in one of its most favourable *milieux*."

A summary of these results is presented in Tables V and VI.

TABLE V.—*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission (Medical Research Council, 1948)*

Radiological Assessment	Streptomycin Group		Control Group	
	No. of Patients	%	No. of Patients	%
Considerable improvement ..	28	51	4	8
Moderate or slight improvement	10	18	13	25
No material change	2	4	3	6
Moderate or slight deterioration	5	9	12	23
Considerable deterioration ..	6	11	6	11
Deaths	4	7	14	27
Total	55	100	52	100

TABLE VI.—*Changes in the Radiological Picture (Medical Research Council, 1948)*

Radiological Assessment	Admission to End of 2nd Month		Admission to End of 4th Month		Admission to End of 6th Month	
	S	C	S	C	S	C
Total patients	55 (100%)	52 (100%)	55 (99%)	52 (99%)	55 (100%)	52 (100%)
Improvement:						
Considerable	8 (14%)	0	25 (45%)	0	28 (51%)	4 (8%)
Slight or mod.	34 (62%)	3 (6%)	18 (33%)	11 (21%)	10 (18%)	13 (25%)
No change ..	7 (13%)	27 (52%)	4 (7%)	9 (17%)	2 (4%)	3 (6%)
Deterioration:						
Slight or mod.	5 (9%)	14 (27%)	4 (7%)	14 (27%)	5 (9%)	12 (23%)
Considerable	1 (2%)	6 (11%)	4 (7%)	8 (15%)	6 (11%)	6 (11%)
Deaths ..	0	2 (4%)	0	10 (19%)	4 (7%)	14 (27%)

S = Streptomycin treated. C = Control.

Draining Cutaneous Sinuses and Fistulae

The ability of streptomycin to produce healing of tuberculous lesions of mucous and serous membranes, extending to lesions which involve the skin and its underlying tissues, was reported to be most remarkable. Prior to its use, cutaneous sinuses usually continued to drain for years. Their surgical treatment and closure were rarely possible. When treated with even small doses of streptomycin most sinuses were found to heal readily. The effect is so striking that it was not even considered necessary to have untreated controls. In the first clinical report of streptomycin therapy all sinuses in three patients healed during treatment. A much more extensive series of cases is summarized in Table VII.

TABLE VII.—*Effect of Streptomycin Upon 382 Patients with 687 Draining Cutaneous Sinuses and Fistulae (From Walker, Hinshaw, and Barnwell—Waksman, 1949)*

No. of Patients	Treatment		No. of Sinuses and Fistulae	Observations at End of Treatment				
	Streptomycin	Days		Healed (Av. 8 wks.)	Imp.	No Change	Worse	Recurrence After Healing
126	1·8–2 g.	120	257	87·3%	7·8%	4·6%	0·3%	2%
229	1 g.	120	403	69·6%	23·5%	6·9%	0	2·5%
15	0·5 g.	120	15	60%	40%	0	0	0
12	0·2 g.	120	12	83%	17%	0	0	0

On the basis of extensive experience in the use of streptomycin in tuberculosis, Walker, Hinshaw, and Barnwell (Waksman, 1949) concluded :

"The introduction of streptomycin into clinical medicine has been peculiarly exciting to phthisiologists. Not only have they never had an 'antibiotic' which was helpful in the treatment of tuberculosis in man, they have never had a proved effective drug of any sort. So far as chemotherapy is concerned, not only was their situation comparable to that of the syphilologist prior to the discovery of penicillin, it was worse than his position before the appearance of Ehrlich and arsenic. Phthisiologists have been dependent on rest in bed, which finds its climax in the 'lung immobilizer,' and, more recently, on collapse therapy,

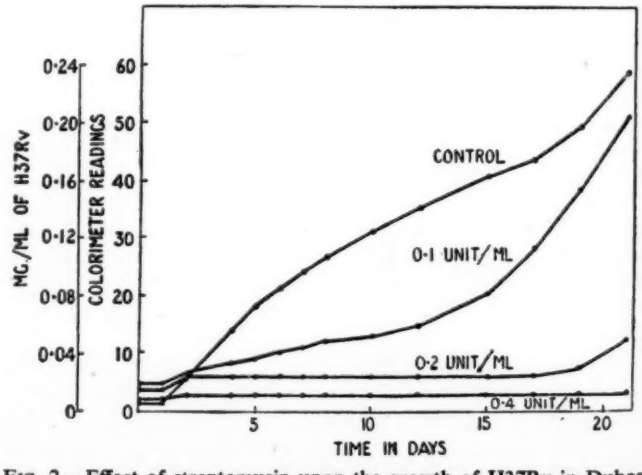


FIG. 2.—Effect of streptomycin upon the growth of H37Rv in Dubos medium (from Steenken and Wolinsky—Waksman, 1949).

which has become most definitive in the form of excisional surgery.

"Chemotherapy is a radical departure from tradition in tuberculosis, and on this account it might have been anticipated that a tuberculostatic drug would be slowly, perhaps inaccurately, evaluated. In the case of streptomycin, this would appear not to have occurred. Within three years after publication of the first clinical paper describing its use, it has been possible to write a chapter of the present sort. This relatively rapid evaluation of a new drug—rapid for tuberculosis if not for pneumococcic pneumonia—is partly the result of experience gained from the investigation of other drugs in other diseases. It is partly a result of the employment, here and in England, of co-operative methods of investigation which have yielded data, reasonably uniform, rapidly, and in large amount; methods which were used, perhaps for the first time, in the beautifully organized study on penicillin and syphilis which was initiated during the recent war."

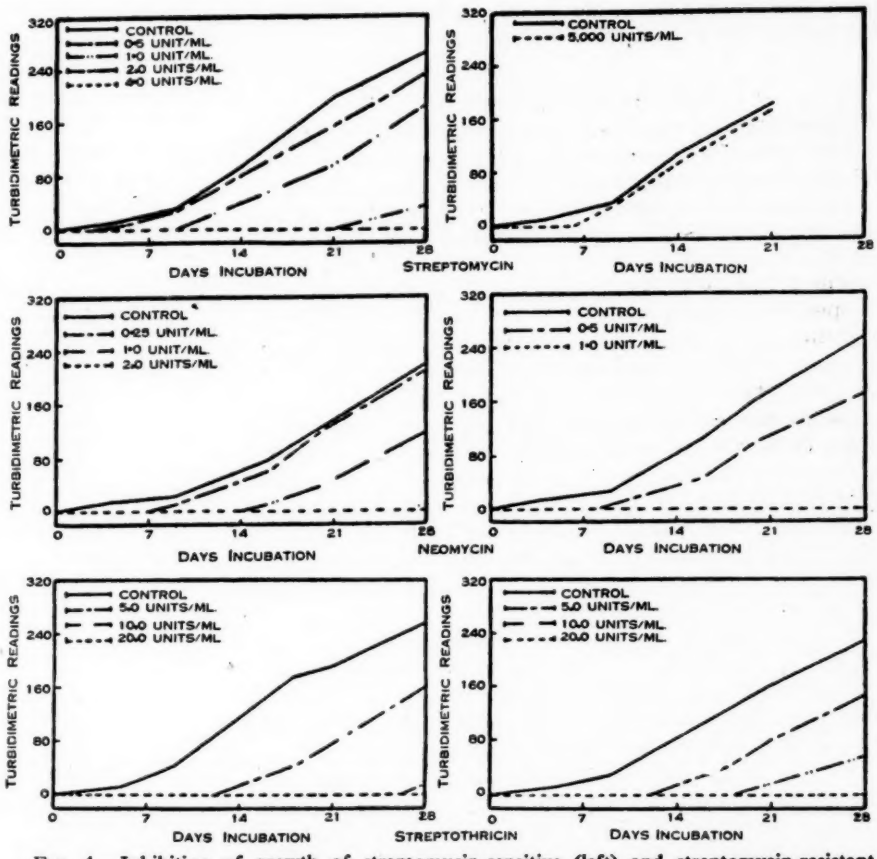


FIG. 4.—Inhibition of growth of streptomycin-sensitive (left) and streptomycin-resistant (right) strains of *M. tuberculosis* H37Rv by three basic antibiotics: upper, streptomycin; middle, neomycin; lower, streptothricin (from Waksman *et al.*, 1949).

Development of Resistance to Streptomycin

Attention has already been directed to the fact that among the most important problems involved in the use of streptomycin in tuberculosis is the development of resistance. This is brought out in a study of the effect of different concentrations of streptomycin upon the rate of growth of *M. tuberculosis* (Fig. 2). Steenken and Wolinsky (Waksman, 1949) emphasized that if the obstacle of streptomycin resistance could only be overcome the efficacy of the drug would be greatly increased. Whether by intermittent administration, or by combination of streptomycin with sulphones or para-aminosalicylic acid, or with some other tuberculostatic agent, it was found possible to delay the onset of streptomycin resistance. By shortening the course of therapy for pulmonary tuberculosis to four or six weeks the incidence of resistant strains is diminished. There is considerable variation in the development of drug-resistant strains in the study of a large group of patients. Those who have definite pulmonary cavitation are more likely to produce resistant cultures than are those without cavitation. Patients who start treatment with a high bacillary count in the sputum show a greater tendency to yield drug-resistant cultures during streptomycin therapy than those with few organisms in the sputum. *M. tuberculosis* lodged in the central nervous system becomes resistant less readily than it does in the lungs.

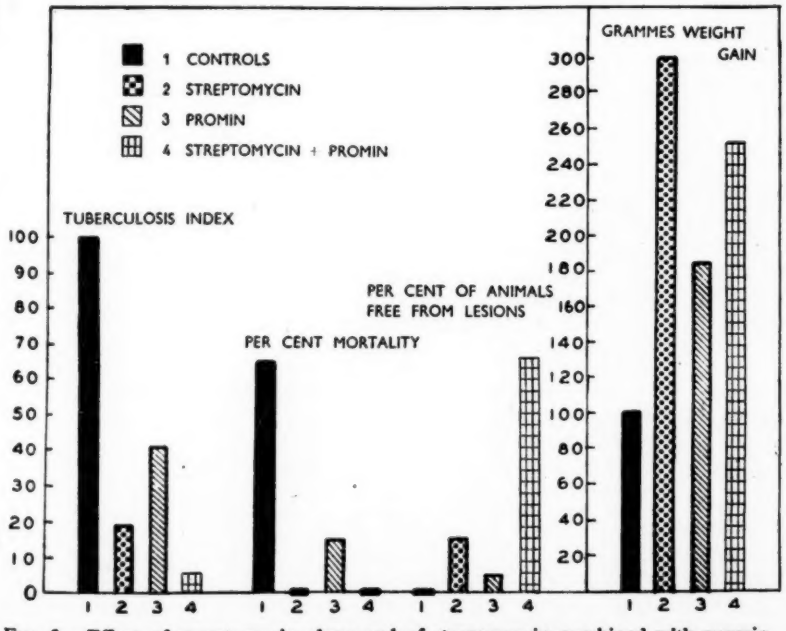


FIG. 3.—Effect of streptomycin alone and of streptomycin combined with promin upon experimental tuberculosis (from Smith and McClosky, 1945).

The possibility of utilizing a combination of two antimycobacterial agents appears, for the present at least, to provide an answer to the problem of development of resistance. This is illustrated in Fig. 3. Another answer may be found in the search for new antibiotics. That this may finally be accomplished is illustrated by the use of neomycin (Fig. 4).

Whether the final solution of the tuberculosis problem will be an antibiotic or a combination of two antibiotics administered together or alternately, such as streptomycin with neomycin, or of an antibiotic and a synthetic compound, only the future can tell. The main conclusion, however, can now be reached: the chemotherapy of tuberculosis is possible. We may only hope that in the near

future this dread disease, the "white plague" of mankind, will become but a memory in the history of man.

Potentialities of Neomycin

Information on the effect of neomycin in experimental and in clinical tuberculosis is still rather scanty. It is difficult to say what this antibiotic will do either in replacing or in supplementing streptomycin. The results presented here are based upon various published and unpublished reports of work done in a number of laboratories in the United States by G. L. Hobby, G. W. Rake, G. Duncan, O. Felsenfeld, and others.

Neomycin possesses a relatively low toxicity for experimental animals, the LD_0 for 20-g. mice being from 750 to 1,500 units. Daily injections of 1,200 to 2,000 units per mouse, administered subcutaneously in divided doses, produced no toxic manifestations. The drug is rapidly absorbed in the body and readily detected in the serum. It is rapidly excreted in the urine. It is highly active in experimental animals, daily dosages of 50 to 110 units per mouse being sufficient to suppress the tuberculous infections. It is just as active against streptomycin-resistant strains as against the sensitive strains.

With regard to the antituberculosis potential of neomycin, it is sufficient to say that in the animals infected with streptomycin-sensitive tubercle bacilli the results of neomycin therapy were, by and large, quite comparable to the results obtained with streptomycin.

One is impressed by the antituberculosis potential of neomycin in experimental tuberculosis against infections induced by either streptomycin-sensitive or streptomycin-resistant tubercle bacilli of the human type, as shown recently by Karlson, Gainer, and Feldman (1950). Until further pharmacological studies exonerate the drug of responsibility for direct or indirect damage to the kidneys, however, its use clinically must be approached with caution.

In human tuberculosis there is an immediate reaction consisting of lowering of the fever and a feeling of well-being. We have not seen toxic reactions with low doses. In two patients there was an increase of the N.P.N. and of the sedimentation rate, which disappeared when the drug was stopped. In some cases, however, definite evidence of a nephrotoxic and ototoxic action was reported.

The results recently published by Karlson, Gainer, and Feldman (1950) brought out the fact that neomycin is capable of producing a reversal of progressive tuberculosis in experimental animals. It is also effective against experimental infections due to streptomycin-resistant tubercle bacilli. A number of clinical cases, representing different forms of tuberculosis, are now being treated with neomycin, and it is expected that before very long a clear picture may be obtained of the potential place that this antibiotic may find in the treatment of tuberculosis. The possibility of combined action of neomycin and streptomycin or another antimicrobial agent is also receiving much consideration.

What of the Future?

The last decade has witnessed considerable progress in the chemotherapy of tuberculosis. From an unknown and questionable possibility, the treatment of this group of diseases by means of chemical agents has become a certainty. The introduction of antibiotics into the field of chemotherapy has opened new potentialities in the eradication of numerous infectious diseases, including tuberculosis. In the case of the latter, streptomycin pointed the way. Announced early in 1944, it has found immediate application in the treatment of various forms of tuberculosis. But streptomycin is not and must not be considered as a cure for tuberculosis.

It has its limitations. Most important of these is its toxic effect upon the eighth nerve and the development of resistance in the infecting agent upon prolonged treatment.

In the search for new antibiotics particular attention has been paid to agents that are more active than streptomycin, that are as active upon the streptomycin-resistant as upon the sensitive strains, and that allow, to a less extent than does streptomycin, the development of resistance. The discovery of neomycin pointed to the possibility of finding such antibiotics. Sooner or later other antibiotics will be found which are more effective than either and less toxic. The fact that in the various surveys on antibiotic production by micro-organisms the acid-fast bacteria are found to be among the most sensitive forms points to the possibility of the existence of such agents. Finding these is merely a matter of further search.

Further possibilities for improving the effect of streptomycin in tuberculosis are found in the combined use of two antibiotics or of an antibiotic and a synthetic compound. We can therefore look forward to a very bright future in the search for chemotherapeutic agents which will prove to be effective in the final eradication of tuberculosis.

REFERENCES

American Trudeau Society (1950). *Amer. Rev. Tuberc.*, **61**, 436.
Council on Pharmacy and Chemistry (1950). *J. Amer. med. Ass.*, **142**, 650.
Fanconi, G., and Löffler, W. (1948). *Streptomycin und Tuberkulose.* Benno Schwabe, Basel.
Feldman, W. H., Hinshaw, H. C., and Mann, F. C. (1945). *Amer. Rev. Tuberc.*, **52**, 269.
Florey, H. W., Chain, E., Heatley, N. G., Jennings, M. A., Sanders, A. G., Abraham, E. P., and Florey, M. E. (1949). *Antibiotics.* Vols. 1 and 2. Oxford University Press, London.
Hinshaw, H. C., and Feldman, W. H. (1945). *Proc. Mayo Clin.*, **20**, 313.
—— —— and Pfuetze, K. H. (1946a). *Amer. Rev. Tuberc.*, **54**, 191.
—— —— —— (1946b). *J. Amer. med. Ass.*, **132**, 778.
Karlson, A. G., Gainer, J. H., and Feldman, W. H. (1950). *Dis. Chest*, **17**, 493.
Medical Research Council (1948). *British Medical Journal*, **2**, 769.
Riggins, H. M., and Hinshaw, H. C. (1949). *Streptomycin and Dihydrostreptomycin in Tuberculosis.* National Tuberculosis Association.
Smith, M. I., and McClosky, W. T. (1945). *Publ. Hlth Rep., Wash.*, **60**, 1129.
Waksman, S. A. (1947). *J. Amer. med. Ass.*, **135**, 478.
—— (1949). *Streptomycin—Its Nature and Practical Application.* Williams and Wilkins Co., Baltimore, Maryland.
—— Hutchison, D., and Katz, E. (1949). *Amer. Rev. Tuberc.*, **60**, 78.

As the result of changes made in the National Hospital Service Reserve since recruiting first opened last autumn, the Ministry of Health has now sent an up-to-date outline of the scheme to all hospital authorities. It has come to the Ministry's notice that some of those who served at first-aid posts in the last war—and would be ready to do so again—have held back from joining the National Hospital Service Reserve because they are under the impression that there will be separate recruiting for first-aid-post personnel. This is not the case. Unlike the arrangements in the last war, the first-aid posts will in future be linked directly to hospitals; therefore personnel for all emergency nursing work, whether in hospital wards or first-aid posts, will be recruited and attached to the hospitals themselves. As far as possible those members joining the Reserve who express a preference to serve at first-aid posts will be earmarked for this kind of work. By the end of June membership of the Reserve had risen to 3,225, made up of 266 trained nurses and 2,959 auxiliaries. In supervising the organization of the Reserve, the Ministry has the guidance of a National Advisory Committee of sixteen members which includes representatives of the hospital authorities, St. John Ambulance Brigade, British Red Cross Society, Association of Hospital Matrons, Royal College of Nursing, and other bodies.

CHOICE OF SULPHONAMIDES FOR MIXTURE THERAPY*

BY

DAVID LEHR, M.D.

Associate Professor, Department of Medicine and Pharmacology, New York Medical College; Associate Attending Physician, Flower and Fifth Avenue Hospitals, New York City

Extensive experimental and clinical studies of the last five years have established the advantages of sulphonamide mixture therapy.[1-17]

In brief the rationale for the use of mixtures is as follows: The renal toxicity of most of the newer sulphonamides, if used singly, is due primarily to over-saturation of the tubular urine with a sparingly soluble sulphonamide and/or its metabolic product, resulting in the formation and deposition of drug crystals in the urinary pathways (crystalluria). This event may be followed by haematuria, oliguria, and complete renal shutdown. If instead of a single sulphonamide a combination of partial dosages of several therapeutically equivalent sulphonamides is employed, the danger of crystal formation in the kidney from the drugs comprising the mixture is significantly reduced. In fact, it will be only as great as if each compound had been administered alone and in the partial dosage contained in the mixture, since sulphonamides of different molecular structure, even if closely related, can be dissolved *simultaneously* to the full extent of their individual solubilities. At the same time full therapeutic potency is retained, since the antibacterial effect of such combinations is completely additive and may in many instances even show potentiation of action *in vitro* as well as at the bedside.[1 2 15]

From the standpoint of renal protection, combinations of substantially equal partial dosages of at least *three* sulphonamides were considered adequate in routine therapy in the absence of alkalization.[18] Some objection has been voiced against the use of mixed sulphonamides on theoretical grounds. It was intimated that the concomitant use of several drugs may lead to the simultaneous development of allergy against more than one component of the mixture.[19] Thus the incidence of allergic reactions might be increased and the possibility of "switching" a sensitized patient to another sulphonamide drug might be eliminated.

This thought was based on the concept that the incidence of sensitization to sulphonamides is largely independent of the dosage used. However, this point of view is not borne out by practical experience. Critical evaluation of the vast literature on sulphonamide therapy[12] demonstrated that, in the dosage range employed in human prophylaxis and therapy, the incidence of sensitization increases in direct proportion with the dosage. Table I shows that, for example, at an oral dosage of not more than 2 to 4 g. of sulphanilamide, sulphathiazole, or sulphadiazine in 24 hours, none of these drugs appeared to produce rash or fever in any significant percentage of cases, even if used for prolonged periods and repeatedly in the same individuals. The incidence of allergic reactions assumed significant proportions only when the daily dosage was increased to more than 4 g. and reached even higher percentages with full therapeutic amounts of 6 g. or more, provided medication was maintained for a minimum of three to five days. These observations indicate that the production of sensitization reactions is dependent upon the repeated presence of certain minimal tissue concentrations of a sulphonamide for a minimum period of several days.

TABLE I.—*Relation of Dosage to Incidence of Sulphonamide Allergy*

Drug	Daily Dosage (g.)	Days of Treatment	No. of Cases Treated	Incidence of Rash and Fever
				%
Sulphanilamide ..	1–2	120–240	188	1·0
	1·5–4	7–21	1,687	0
	6–9	5–10	1,407	>10·0
		Routine therapy		7·2*
Sulphathiazole ..	2–4	3–15	3,584	0
	6	3–10	2,475	>6·4
	6–10	5–10	529	>10·0
		Routine therapy		11·2*
Sulphadiazine ..	1	12–90	664,840	<0·5
	2–4	3–20	18,185	0·07
	4–6	7–14	500	1·8
	6+	2–31	2,791	2·3
		Routine therapy		2·9*

* These figures are based on a comprehensive compilation of the incidence of rash and fever reported in the literature.

In most patients sensitization is specifically limited to the sulphonamide used. Hence the simultaneous administration of several sulphonamides in *partial* dosage may result in a reduced rather than an increased incidence of sensitization because mixtures permit "dilution" of individual drug concentrations below the level necessary for the production of allergy.

This concept appeared to be substantiated by our experience with more than 700 patients treated with combinations of two or three sulphonamides, including sulphadiazine, sulphamerazine, sulphapyrazine, sulphacetamide, and the "worst offender" sulphathiazole. The incidence of drug rash and fever at the full therapeutic dosage of 6 g. in 24 hours was impressively low and nowhere exceeded 2%.[12]

It has yet to be established whether closely related compounds such as isomers and homologues —e.g., sulphadiazine, sulphapyrazine, sulphamerazine, and sulphamezathine (sulphadimidine)—can be distinguished by the cells of the body as specific haptens. Should they prove indistinguishable, the danger of sensitization from their combined partial dosages could still not be greater than if the equal total amount of any one of these drugs had been employed. Hence no *increased* incidence of allergic reactions should result from any sulphonamide mixture, so long as individual drug concentrations in the tissues are kept well below the level usually necessary for the production of sensitization.

Theoretical Considerations

It seemed of interest to compare some properties of systemic sulphonamides which might help to determine their relative desirability as components of mixtures.

TABLE II.—*Relation of Solubility to Renal Complications*

Drug	Symbol	Solubility in Water 37° C.; pH 5·5 (Mg./100 ml.)		Blockage of Kidneys by Crystalline Deposits
		Free	N_4 Acetyl	
Sulphadiazine ..	SD	13	20	Frequent
Sulphamerazine ..	SMD	37	79	"
Sulphamezathine	SMMD	75	115	Rare
Sulphapyrazine ..	SPZ	5	5	Very frequent
Sulphathiazole ..	ST	98	7	" "
Sulphacetamide ..	SAC	1,100	215	Not encountered
Sulphanilamide ..	SA	1,500	530	" "

*This investigation has been made with the assistance of grants from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association, and the Schering Corporation, Bloomfield, N.J. A paper to be read at the first International Congress of Internal Medicine, Paris, September 11–14, 1950.

Table II represents an enumeration of systemic sulphonamides which deserve consideration for possible use as combinations. (The symbols for the different drugs shown here will be used in all subsequent graphs and tables.)

It is readily apparent that a definite relationship exists between the solubility of the sulphonamides and their acetylated metabolites and the frequency of renal complications. From this point of view sulphapyrazine would seem to be about the least desirable and sulphacetamide and sulphanilamide the most advantageous compounds. However, the high solubility of sulphanilamide is outweighed by its considerable overall toxicity. For this reason sulphanilamide was not used in our studies.

The behaviour of the other six drugs in the human body, as gleaned from the extensive literature on this subject, is illustrated in Table III. The desirable features of each drug are there stressed by bold print. Distinct drawbacks are indicated by italics. It can be seen that sulphadiazine is the least plasma-bound, best-diffusing, and least acetylated of the four "diazines." Hence, sulphadiazine rightfully maintains a therapeutic advantage over sulphamerazine and a definite superiority over sulphamezathine and sulphapyrazine. Sulphathiazole shares the disadvantage of excessive plasma-binding with the three last-named drugs and manifests in addition particularly poor diffusion into the cerebrospinal canal. Sulphacetamide, on the other hand, except for low blood levels due to rapid excretion, exceeds even the merits of sulphadiazine with regard to conjugation, diffusion, and plasma-binding.

TABLE III.—*Comparison of the Behaviour of Six Sulphonamides in the Human Body*

Drug	Average Blood Levels* Free Sulphonamide Mg./100 ml.	% Plasma-bound	Diffusion into C.S.F. (% of Blood Level)	% Acetylated in the Body
SD	**8–15**	**17–58**	**50–75**	**20–40**
SMD ..	**10–20**	*39–84*	30–60	30–60
SMMD ..	**5–12**	*39–84*	30–60	*50–80*
SPZ	**5–12**	00–50	40–60	*50–85*
ST	**4–7**	*60–75*	*10*	**10–30**
SAC ..	**5–10**	**13–20**	**60–85**	**20–40**

* At a daily maintenance dose of 6 g. orally. Bold type = Advantages. Italic figures = Drawbacks.

No substantial differences seem to exist among systemic sulphonamides concerning their antibacterial spectrum. It should be remembered that various sulphonamides possessing a free para-amino group do not display appreciable differences in bacterial affinities. Molecular changes in the N_1 substituent serve to modify quantitative rather than qualitative antibacterial properties.[20]

In the animal experiment sulphathiazole proved the most toxic of the group, closely followed by sulphapyrazine, and then sulphadiazine and its two methyl homologues, which are about equally as toxic, whereas sulphacetamide is about five times less toxic than sulphadiazine.[21]

From a clinical point of view it can be assumed as established that, on the basis of their excellent clinical record, sulphadiazine and sulphamerazine qualify at present for first and second place respectively as components of any mixture. The other four compounds deserve attention as possible *additional* members of a combination.

Experimental Results

With this view in mind, I compared various triple mixtures with regard to antibacterial activity, toxicity, and therapeutic effectiveness in the experimental animal and in man. The majority of the mixtures contained both sulphadiazine and sulphamerazine as constant components, whereas the third component varied between sulphamezathine, sulphapyrazine, sulphathiazole, and sulphacetamide. Most experimental procedures used were closely similar to those outlined previously in detail.[2,7] For the sake of conciseness their description was eliminated from the present report.

No substantial differences were observed with any of the mixtures studied concerning *in vitro* antibacterial activity and efficacy against experimental infections of mice. On the whole the triple mixtures proved about equally as effective as sulphadiazine in identical total concentration or dosage.

Absorption, fate in the body, and excretion of these triple mixtures were investigated in rats, rabbits, and human beings. The results of representative experiments on tissue distribution in groups of albino rats are summarized in Figs. 1 and 2.

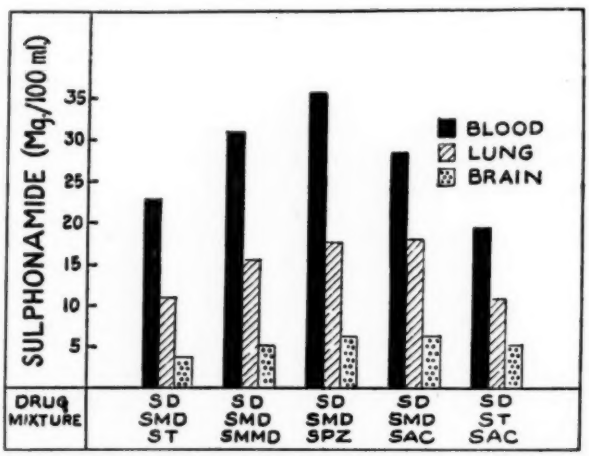


FIG. 1.—Concentrations of sulphonamide mixtures in tissues (single administration in albino rats).

Fig. 1 demonstrates the relationship of the drug concentrations in blood, lungs, and brain three hours after a single oral intubation of five triple mixtures (0.5 g./kg.). Although the sulphapyrazine and sulphamezathine combinations show higher blood levels, the sulphacetamide mixture, which is a close third in this respect, stands out as the one with excellent tissue distribution. In fact, the diffusion of this drug mixture into lungs and brain slightly surpasses that of the sulphapyrazine combination and is distinctly higher than that of the sulphamezathine or sulphathiazole mixture.

Similar results were achieved in 70 rabbits in studies of tissue distribution of sulphonamides from various routes of administration. In addition spinal fluid was obtained in these animals by occipital puncture, so that the blood–spinal-fluid ratio could be calculated. From the oral route of administration the diffusion of the sulphadiazine–sulphamerazine–sulphacetamide mixture through the haematocephalic barrier was as good as that of sulphadiazine, and the absolute concentration in the spinal fluid and blood even somewhat higher than that from sulphadiazine alone.

In the chronic study (Fig. 2), groups of rats were examined in a similar fashion after having been fed a standard diet containing 0.5% of four triple mixtures for 14 days. Here the mixture containing sulphamezathine as third component produced the lowest sulphonamide concentrations in lungs and brain, whereas there was no substantial difference between sulphathiazole, sulphapyrazine, and sulphacetamide in this respect. Since sulphathiazole

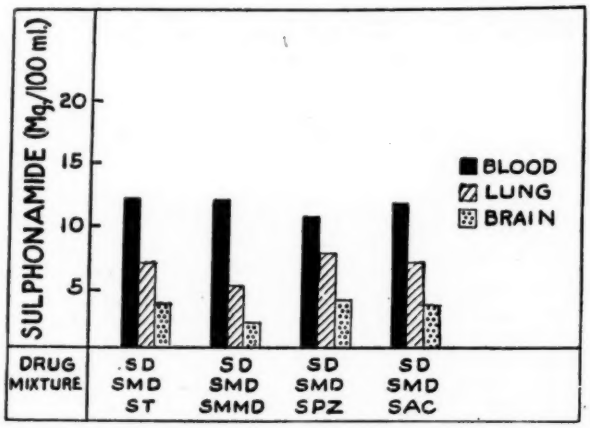


FIG. 2.—Concentrations of sulphonamide mixtures in tissues (chronic administration in albino rats).

has fallen into disfavour[22] and sulphapyrazine possesses a rather high experimental and clinical toxicity,[23] the mixture containing sulphacetamide appeared the most desirable composition for immediate clinical application.

This viewpoint was strengthened in numerous studies of absorption and excretion in 60 human subjects, using single and multiple dosages of separate and mixed sulphonamides. Tables IV and V represent a summary of all single-dose experiments with separate drugs and drug mixtures.

TABLE IV.—*Absorption and Excretion of Single Sulphonamides in Man**

Drug	Blood				Urine	
	Free Drug Mg./100 ml.				Total Drug Excreted After 24 Hours	
	1 Hr.	4 Hrs.	8 Hrs.	24 Hrs.	Mg.	% of Dose
SD ..	1·8	8·0	7·2	3·7	2,223	55·5
SMD ..	3·0	9·8	9·0	4·7	1,077	26·9
SMMD	4·2	7·8	5·1	2·6	1,233	30·4
ST ..	3·9	6·5	5·0	1·0	2,869	71·7
SAC ..	6·2	6·8	4·5	1·4	2,801	71·0

* Each figure represents the mean of the values of 4 or more male test subjects. The dose was 4 g. sulphonamide orally.

Table IV illustrates on the left the blood levels achieved in groups of four male subjects with five single sulphonamides and on the right the total amount of drug excreted in 24 hours in mg. and as percentages of the 4-g. dose. It is apparent that sulphacetamide and sulphathiazole show the fastest absorption and most complete excretion, and that within the four-hour interval the blood levels of sulphacetamide are better than those of sulphathiazole and not far behind those of sulphamezathine. This is the more significant since sulphamezathine, like sulphamerazine, shows very incomplete urinary excretion, a fact which could be partially accounted for by their greater retention in the blood stream (plasma-binding) and partially by poorer absorption after oral administration. The percentage of acetylation was highest for sulphamethazine (68%), followed by sulphamerazine (46%), sulphadiazine (33%), sulphacetamide (30%), and sulphathiazole (21%). The behaviour of three triple mixtures under identical experimental conditions is depicted in Table V.

It is apparent that the replacement of sulphathiazole by sulphacetamide as the third component tends to raise blood levels slightly within the first four hours and to lower them accordingly thereafter. Sulphamezathine in the same position assists, as expected, in the prolonged maintenance of high levels and greatly retards urinary excretion. Conjugation of all three mixtures within the first 24 hours was around 30–40%, which was less than could be expected on the basis of mathematical computation using the figures of the single drugs. Since, in our hands, a combination of sulphadiazine–sulphamerazine–sulphathiazole had given excellent therapeutic results at the bedside, it was expected that the replacement of sulphathiazole by sulphacetamide would not interfere with the therapeutic efficiency of the triple mixture.

TABLE V.—*Absorption and Excretion of Sulphonamide Mixtures in Man**

Drug Mixture (Equal Parts)	Blood				Urine	
	Free Drug Mg./100 ml.				Total Drug Excreted After 24 Hours	
	1 Hr.	4 Hrs.	8 Hrs.	24 Hrs.	Mg.	% of Dose
SD+SMD+ST	4·4	11·4	9·2	3·5	2,350	58·7
SD + SMD + SMMD ..	4·2	10·1	10·5	5·1	1,616	40·3
SD + SMD + SAC	6·3	9·2	7·1	3·2	2,431	60·7

* Each figure represents the mean of the values of 4 or more male test subjects. The dose was 4 g. sulphonamide orally.

Clinical Application of Triple Mixtures

Clinical trials with a combination of equal partial amounts of sulphadiazine–sulphamerazine–sulphacetamide have been completed. A total of 170 unselected patients of all age groups with serious acute infections have undergone this therapy at the full routine dosage (in children: 0.15 to 0.2 g./kg. body weight daily; in adults: 3–4 g. initially, 4–6 g. daily thereafter; the lower maintenance dose of 4 g. daily proved adequate in most instances). Blood levels were excellent. They ranged as a rule between 10 and 25 mg. of free sulphonamide per 100 ml. Acetylation was low, rarely exceeding 20–25% in the blood and 40% in the urine. Although no alkalizing agents were used, crystalluria of a moderate degree was encountered in only 12 instances, as a rule in connexion with excessive urine concentrations of sulphonamide. There were two cases of drug rash and fever occurring on the tenth and the thirteenth day of therapy, respectively, and two instances of fever alone, possibly due to sulphonamide administration. One patient with acute tonsillitis had severe nausea and vomiting on the third day of drug administration, requiring interruption of therapy, and another patient with pneumonia developed a moderate degree of "cyanosis" apparently due to the drug. No other serious untoward reactions were observed.

Therapeutic results were highly satisfactory, with defervescence usually occurring within the first 24 to 48 hours. The series comprised 55 cases of bacterial pneumonia, 23 of shigellosis (*Shigella sonnei*), six of pyelitis, five of bacterial meningitis, one of penicillin-resistant pneumococcal bacteriaemia, and one of penicillin- and streptomycin-resistant staphylococcal septicaemia.

The experimental and clinical evaluation of other sulphonamide mixtures is continuing at present.

Summary

The simultaneous administration of several sulphonamides in *partial* dosage may result in a reduced rather than an increased incidence of sensitization, because mixtures permit "dilution" of individual drug concentrations below the level necessary for the production of allergy. Hence it is possible to enhance the renal protection afforded by sulphonamide mixtures by using additional components in proportionately smaller amounts, without the danger of increasing the incidence of allergic reactions.

Sulphadiazine and sulphamerazine qualify for first and second place, respectively, as mixture components. Sulphathiazole, sulphapyrazine, sulphamezathine, and sulphacetamide deserve attention as possible third and fourth members of a combination. Although sulphathiazole has fallen into disfavour in the U.S.A. because of its high clinical toxicity, mixtures containing this drug have shown a low overall toxicity. Sulphapyrazine, the most insoluble of these compounds, induces frequent renal and allergic reactions and therefore offers no advantages over sulphathiazole. Sulphamezathine has adequate solubility and low toxicity, but is subject to substantial conjugation and plasma-binding, which diminish its therapeutic efficiency. Sulphacetamide retains the high solubility of sulphanilamide and shares with the parent compound the improbability of renal concretion formation and the ready diffusibility into all tissues. In addition, it shows low figures for conjugation, plasma-binding, and sensitization.

The mixture sulphadiazine–sulphamerazine–sulphacetamide (equal amounts) revealed low toxicity in animals as well as excellent bacteriostatic activity *in vitro* and in experimental infections of mice. After oral administration, blood and spinal-fluid levels were similar to those from equal doses of sulphadiazine or sulphamerazine. Clinical trials of this mixture in 170 patients with acute systemic infections showed a high curative value and low toxicology.

REFERENCES

[1]Lehr, D. (1945). *Proc. Soc. exp. Biol., N.Y.*, **58**, 11.
[2]—— (1946). *J. Urol.*, **55**, 548.
[3]Frisk, A. R., Hagerman, G., Helander, S., and Sjögren, B. (1946). *Nord. Med.*, **29**, 639. Idem (1947). *British Medical Journal*, **1**, 7.
[4]Lehr, D., Slobody, L. B., and Greenberg, W. (1946). *J. Pediat.*, **29**, 275.
[5]Flippin, H. F., and Reinhold, J. G. (1946). *Ann. intern. Med.*, **25**, 433.
[6]Nilzen, A. (1946). *Svenska Läkartidn.*, **43**, 1816.
[7]Lehr, D. (1947). *Proc. Soc. exp. Biol., N.Y.*, **64**, 393.
[8]Snyder, L. J. (1947). *J. Lab. clin. Med.*, **32**, 1532.
[9]Lehr, D. (1947). *British Medical Journal*, **2**, 943.
[10]Sjögren, B., and Ortenblad, B. (1947). *Acta chem. scand.*, **1**, 605.
[11]Slobody, L., Lehr, D., and Willner, M. M. (1948). *Pediatrics*, **2**, 58.
[12]Lehr, D. (1948). *British Medical Journal*, **2**, 543.
[13]Oettinger, L., and Cronheim, G. (1948). *Amer. Practit., Phila.*, **2**, 526.
[14]Ledbetter, J. H., and Cronheim, G. E. (1948). *Amer. J. med. Sci.*, **216**, 27.
[15]Shore, P. D., Flippin, H. F., and Reinhold, J. G. (1949). Ibid., **218**, 80.
[16]Johnson, P. B. (1949). *Sth med. J.*, **42**, 761.
[17]Lehr, D. (1950). *N.Y. St. J. Med.*, **50**, 1361.
[18]—— (1949). *J. Amer. med. Ass.*, **139**, 398.
[19]Carrol, W. (1948). *Ann. intern. med.*, **29**, 533.
[20]Goldstein, A. (1949). *New Eng. J. Med.*, **240**, 98.
[21]Lehr, D. (1945). *J. Urol.*, **54**, 87.
[22]Council on Pharmacy and Chemistry (1949). *J. Amer. med. Ass.*, **141**, 264.
[23]Northey, E. H. (1948). *The Sulfonamides and Allied Compounds*, pp. 575, 577. Reinhold Publishing Corporation, New York.

Over 200 Scottish nurses had their names added to the *Register* of the General Nursing Council for Scotland on June 21. New rules made by the Council provide for the transfer of these nurses from the 1943 Nurses' List to the *Register* without application or payment of fee. This allows these nurses, who have hitherto been known as State-listed nurses, to be classified as State-registered in the branch of nursing in which they are qualified. It also grants them the right to vote in the forthcoming elections for the new General Nursing Council. The rules provide that persons who would have been eligible for admission to the 1943 list but who did not apply within the prescribed period may also be admitted to the *Register*. In their case, however, application for admission must be made to the registrar of the council.

MEDICAL TREATMENT OF HYDATID CYSTS OF LUNG*

BY

MARIANO R. CASTEX, M.D.

AND

EDUARDO L. CAPDEHOURAT, M.D.

Pulmonary hydatid cysts, apart from the rare cases which heal spontaneously after a single or repeated expectoration, are exclusively in the domain of surgery, varying only in the details of technique suited to each case.

Encouraged by the good results obtained in severe broncho-pulmonary suppurations, both localized and diffuse, by our method of transthoracic intrapulmonary injections of sulphonamides, antibiotics, and other drugs, we extended this treatment to suppurations due to the retention of hydatid membranes—that is, to suppurating cysts of the lung with incarcerated membranes. A few years later, in view of our favourable experience with infected cysts, we applied the same method of treatment to clean uninfected hydatid cysts.

Without exaggeration, and on the basis of our case records, we can now say that some cases can be treated medically. The importance and scope of this treatment remain to be established by further experience. Whilst the results in cases followed up have so far been successful, their number is too small to warrant definite conclusions. Nevertheless, we are optimistic, since we cannot believe that only the favourable cases came into our hands.

These cases fall into three categories : (1) suppurating pulmonary hydatid cysts, with retained membranes; (2) ruptured pulmonary hydatid cysts, with loss of fluid content and persistence of the parasitic cavity, whether air-containing or not; and (3) hyaline hydatid cysts—that is, closed and non-infected. We will outline the therapeutic procedures employed in each category, and give a single example of each kind to show the more salient clinical features.

Suppurating Pulmonary Hydatid Cysts, with Retained Membranes

These cases present two problems : broncho-pulmonary suppuration and the retention or incarceration of the parasitic membranes. The first problem is really a consequence of the second, since the membranes, except in rare instances of clean encystment or of calcification, behave as true foreign bodies, leading sooner or later to pus formation in the surrounding parenchyma.

We treat pulmonary suppuration locally by means of transthoracic injections of sulphonamides and antibiotics, choosing the drug according to the organism isolated, whenever possible, from the material aspirated, and adapting the dosage, interval of administration, etc., to the clinical and radiological progress of the patient.

The complete expulsion of the membranes, which is essential to end the suppuration, is achieved by a purely mechanical effect. The local congestion, partly hydrostatic and partly biochemical, created by the transthoracic injection provokes intense and repeated bouts of coughing, which directs the fluid current towards bronchi already dilated as a result of the suppuration. This flow carries along with it fragments of endocyst which have been

*A paper to be read at the First International Congress of Internal Medicine, Paris, September 11–14, 1950.

detached as much by the intense cough as by the proteolytic ferments of the pyaemic organisms. The insertion of the needle into the parenchyma, as well as the jet of solution, helps to break up the membrane and facilitate its expulsion. It is noteworthy that in most cases cyst remnants thus ejected were expelled during or shortly after injection; this seems to establish a cause-and-effect relationship between the local influx of the drug and the expulsive action that follows it. In our cases the mechanical action achieved by the intrapulmonary injection has shown itself to be superior to bronchoscopic suction, which proved completely ineffective in all our cases, though performed by an experienced operator several times on one patient.

When all parasitic remains have been expelled and the broncho-pulmonary infection has died down, healing occurs rapidly; this includes the whole bronchial tree draining the affected area, as demonstrated by clinical and radiographic examination. In some cases a slight increase in pleural opacity remains, with deformity of the diaphragm and obliteration of the costodiaphragmatic recess in the case of basal cysts, sequelae which do not affect the working capacity of the lung or the efficiency of the patient in carrying out normal activities.

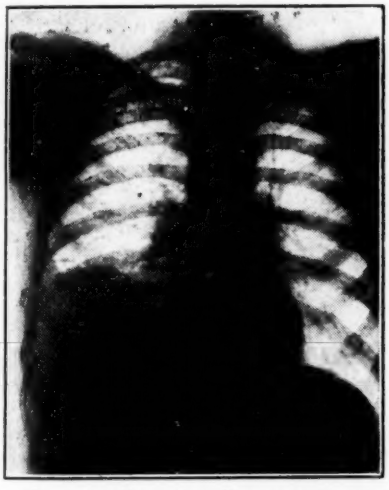


FIG. 1.—Case 1. The opaque cyst occupying the base of the right lung. A slight reaction is present.

FIG. 2.—Case 1. The cystic shadow is in the lowermost segment of the right lower lobe.

Case 1

A single labourer aged 41 was suffering from a suppurating hydatid cyst in the right lower lobe (Figs. 1 and 2). He was treated in the out-patient department and was thus able to remain on light work throughout treatment.

In view of the long history and the size and superficial location of the cyst, it was punctured at once at its most accessible point, which corresponded to the postero-inferior region of the lobe.

Hydatidocentesis was carried out without the slightest inconvenience, immediate or remote. The first punctures yielded a small quantity of very thick pus and were then followed by 27 intrapulmonary injections. The first contained 200,000 units of crystalline sodium penicillin in 20 ml. of isotonic glucose saline; most of the others contained 100,000 units in the same volume. Two injections consisted of an ampoule of "prontosil" mixed with an ampoule of "cibazol," and the last two injections consisted of 100,000 units of penicillin and an ampoule of cibazol and an ampoule of prontosil respectively. Treatment began on June 13, 1947, and ended on August 23 of that year, the intervals having varied from one to three days at the beginning and from four to twelve days towards the end. The cyst membrane was expelled in fragments during the course of the treatment. The good result obtained is clearly shown in Figs. 3 and 4.

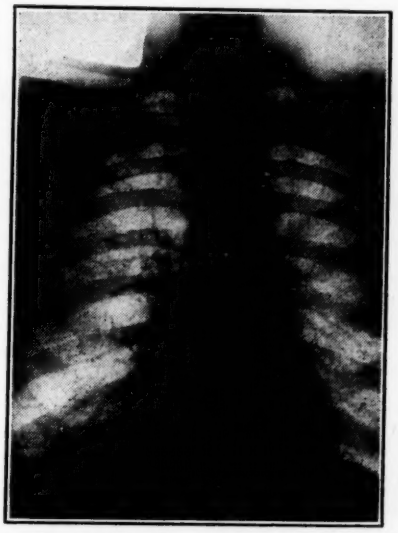


FIG. 3.—Case 1. Disappearance of the cystic shadow, and absence of any remnant of membrane.

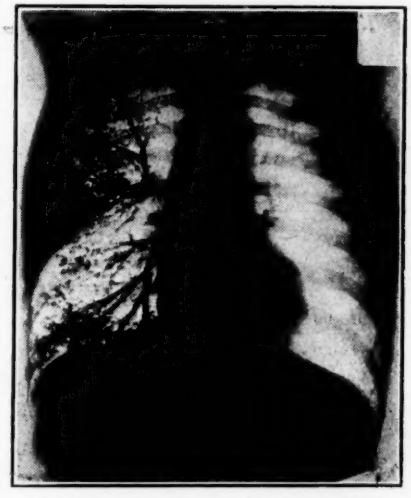


FIG. 4.—Case 1. Bronchogram showing the normal bronchial tree in the area previously occupied by the cyst.

Hydatid Cavities, Whether Air-containing or Not

In these cases, after rupture of some cysts, treatment is aimed essentially at removing the retained parasitic membrane which lines the cavity. This is achieved over a certain time, usually several months, by injection of digesting solutions containing hydrochloric acid and pepsin. Hydatid membrane, when exposed to these substances, becomes appreciably thinned and can then be coughed up without great efforts. This structural change is easily demonstrable by comparing the eliminated fragments with membrane which has not been exposed to digestive action. Patients show complete tolerance to the digestive solution, and this allows the frequent injections rendered necessary by the fact that the solution acts only for a short time because of rapid elimination, reabsorption, or both, and because of its dilution.

Case 2

A single labourer aged 34 had a ruptured hydatid cyst with air in the residual cavity situated in the left postero-inferior lobule. He was given intracystic injections of 10 ml. of a solution of pepsin in hydrochloric acid, the concentration of pepsin varying between 5 and 20%, and the HCl from 0.05 to 0.15%.

After 30 injections over a period of three months, and following complete expulsion of the parasitic membrane and consequent obliteration of the cavity, he was discharged healed. The digestive action had visibly affected the chitinous membrane, the expelled fragments being reduced to thin wafers which had lost their characteristic tendency to form cylinders. Erosion of the membrane facilitated its fragmentation and subsequent expectoration.

Hyaline Hydatid Cysts

These are referred to as clean, because they are closed and non-infected; they require a more complex treatment as follows: (1) Desensitization of the patient by injection in increasing doses of hydatid fluid and of its antigen, along the lines suggested by its discoverer, Dr. B. Calcagno. This is to prevent anaphylactic shock which, as is known, may be severe or even fatal. According to Calcagno this measure brings on death of the hydatid and so deprives it at the time of opening of its toxic properties on absorption of the hydatid fluid. (2) Fixation of the cyst to the chest wall, if this has not already occurred. This requires: (*a*) the induction of a pneumothorax; (*b*) irritation of the pleura by the use of substances such as hypertonic glucose or saline solutions, cibazol, 5% sodium morrhuate or ricinoleate urethane, etc., after previous injection of about 2 ml. of 0.5 to 2% procaine to allay pain and prevent reflex manifestations; (*c*) re-expansion of the lung; and (*d*) confirmation of pleural adhesion over the area by the failure of repeated attempts at fresh pneumothorax. (3) Puncture of the cyst, or hydatidocentesis. (4) Gentle aspiration of part of the hydatid fluid. (5) Chemical sterilization of the cyst by instilling some 10 to 20 ml. of 2% formalin and allowing it to stand for ten minutes. (6) Complete evacuation of the cyst.

There are now two alternative courses. One is similar to the treatment of a hydatid cavity and relies on the use of digesting substances. The other, which is much longer, is to await suppuration as a result of the retained membranes, or to induce it by such means as injection of terebene oil; induction of suppuration, however, is difficult to achieve because of the diffusion and absorption of the injected fluid. When suppuration is established, treatment is carried out as for the first category, in which infection pre-existed.

Expectoration of the intact membrane after emptying the cyst by puncture remains for us only a theoretical possibility, since we have never seen it happen. This could be explained by the disparity between the size of the membrane and that of the bronchial lumen, so that passage of the former is impossible even in the most severe bouts of coughing, whether or not induced by intrapulmonary transthoracic injection.

On the other hand, expectoration of the endocyst occurs reasonably easily and within a relatively short period after intrafocal medication when pulmonary suppuration is present, since the latter dilates the bronchial lumen at the same time as it fragments the parasitic membrane.

Case 3

A married woman aged 30 had a hydatid cyst in the left postero-inferior lobule. Pneumothorax was first induced, later followed by the intrapleural injection of 25 ml. of 50% glucose solution containing one ampoule of cibazol. Another sclerosing solution, "neo-varisclerin," was run in on three subsequent occasions, and the lung was then helped to re-expand by aspiration of the pneumothorax. All this took four months, during which time the patient was also undergoing desensitization with an antigen prepared by Dr. Pirosky, following Dr. Calcagno's method, according to whom this procedure should kill the cestode.

Failure to reinduce pneumothorax having demonstrated the pleural adhesion, the cyst was punctured without mishap. Then 20 ml. of fluid was drawn off and replaced by 10 ml. of 2% formol. Ten minutes later a similar amount was extracted and a further 10 ml. of 2% formalin was run in. As a final step, total evacuation of the cyst was attempted by carrying out injections into the cavity, some of penicillin and some of sulphonamides ("rubiazol" and prontosil), over a period of two months. After an interval of air-distension, the cyst collapsed and incarcerated the membrane.

Months later, since the patient had not managed to cough up the membrane, suppuration of the surrounding lung parenchyma was induced by the injection of terebene oil and the patient was temporarily discharged until the suppuration had become established some six months later. At this stage amounts of 20 to 40 ml. of physiological saline were injected into the area to act purely mechanically by causing coughing and subsequent expectoration. Five injections in six days were enough to achieve the complete expulsion of the parasitic membrane followed by the almost immediate subsidence of the pulmonary infection despite the fact that no active therapeutic substance had been used. This supported the belief that the pulmonary suppuration was caused mainly by the retained endocyst acting as a foreign body.

Conclusion

We consider that this method of bloodless treatment which we have devised is worthy of trial in strictly selected cases of hydatid cyst before deciding in favour of surgical intervention, which should remain a last resort.

The advantages of the method are: (1) It can be completely effective. (2) It does no injury to the body, whether locally or systemically. (3) It does not hinder the recovery of the affected broncho-pulmonary area. (4) It carries less risk than operative methods, which involve loss of blood and some mutilation. (5) It can be carried out on outpatients, to the advantage of either the State or the individual, who is spared the expense, and of the family, whose breadwinner can with care engage in some forms of light work without prejudicing his recovery. This double advantage of ambulant treatment would compensate for the longer time that is sometimes required for medical treatment as compared with surgical methods, particularly since the latter may also occasionally be prolonged by unfortunate complications. (6) It is no bar to subsequent operative treatment, which should be held in reserve in case of failure of this bloodless method.

RECENT ADVANCES IN OUR KNOWLEDGE OF THE MALARIA PARASITE*

BY

H. E. SHORTT, C.I.E., M.D., F.R.S.

Professor of Medical Protozoology, London School of Hygiene and Tropical Medicine

The demonstration by James and Tate (1938) of the essential part played by the exo-erythrocytic forms in the life cycle of *Plasmodium gallinaceum* started an intensive search for similar forms in the case of mammalian and human malaria parasites. The subsequent demonstration of the pre-erythrocytic forms of this parasite (Mudrow, 1940; Shortt, Menon, and Iyer, 1940; Huff and Coulston, 1944) intensified the search for similar pre-erythrocytic forms in simian and human malaria.

The investigation was taken up by malariologists in Europe, America, Asia, and Africa, and various findings were reported, none of which secured general recognition. A critical survey of these results was made by Angelini (1947), who came to the conclusion, subsequently justified, that none of the claims had been substantiated. This was the position when Fairley (1945, 1947) described the results of his classical experiments at Cairns with human volunteers infected with *P. vivax* and *P. falciparum* by the bites of

*To be read at the First International Congress of Internal Medicine, Paris, September 11–14, 1950.

infected mosquitoes. The results of these experiments, which cannot be described in detail, demonstrated the inescapable conclusion that during the incubation period of malaria after infection by mosquitoes the parasites which develop from the sporozoites must undergo some form of development, preliminary to invading the erythrocytes, in a secluded situation outside the circulating blood. This was a sure foundation on which to base the search for pre-erythrocytic forms.

The monkey parasite, *P. cynomolgi*, readily transmissible by *Anopheles maculipennis*, and closely resembling *P. vivax* of man, provided the most convenient material for study. All attempts, however, to demonstrate pre-erythrocytic forms proved abortive, and some observers cast doubts on their existence, while others considered that the methods being used in the search were faulty and that some new approach to the problem was indicated.

I had come to the conclusion, however, that the cause of failure by all workers, including myself, to demonstrate pre-erythrocytic forms of mammalian plasmodia was the use of inadequate numbers of infective mosquitoes in individual experiments. For this reason a crucial experiment was carried out in which 576 infected mosquitoes were fed upon a single rhesus monkey and the entire number of mosquitoes ground up and inoculated into the same animal.

Development of Pre-erythrocytic Forms

The monkey was killed seven days later and material from practically every type of tissue taken for study. The examination of this revealed, in the liver only, the long-sought pre-erythrocytic stage of a mammalian malaria parasite. Following this technique, it has been possible to demonstrate the development of these pre-erythrocytic forms from their early stages to maturity. The details of this development are as follows.

The earliest form so far found is a parasite seen four days after infection of the monkey by mosquitoes. It is situated inside a parenchyma cell of the liver, close to the nucleus. The original nucleus of the parasite has divided to produce 20 or more nuclei, so the parasite may now be called a schizont. From the fourth to the ninth day the parasite increases in size, while the nuclei multiply progressively until by the eighth or ninth day there are certainly over 1,000. The liver cell by this time is a mere bag containing the parasite, which may be 35 to 40 μ in diameter. The nucleus of the liver cell is pushed to the periphery of the body. The general shape of the schizont is ovoid, but lobose arms may be produced, probably due to unequal expansion in the direction of least resistance. In many cases vacuoles, single or multiple, appear in the body of the schizont.

There now follows condensation of the parasitic cytoplasm around the nuclei to form merozoites, which in a mature schizont number well over 1,000. Each is a small ovoid body about 1.1 μ in diameter with a single nucleus often eccentric in position. The containing cell membrane now ruptures and releases the merozoites into the surrounding tissues or into a blood sinusoid. Up to this point there has been no reaction on the part of the liver to the foreign body. On rupture of the latter, however, there is an immediate invasion of the area by phagocytic cells. The majority of the merozoites probably now invade erythrocytes to produce the blood infection, but many are engulfed by the phagocytes and destroyed.

Some of the merozoites almost certainly reinvade other parenchyma cells and recommence the cycle which has been described. This cycle can go on in the liver independently of the blood cycle, and is the probable cause of relapses in malaria. In proof of this a monkey which had been infected three and a half months previously, and in which the primary development from sporozoites must long have been completed, was examined. This monkey had shown no parasites in the peripheral blood for a month, and an early relapse was considered probable. On examination of the liver, exo-erythrocytic forms were found similar to those previously described.

The following interpretation of the cause of relapses is offered for consideration.

When an animal has been infected for some time it acquires an active immunity which is capable of destroying the merozoites produced either in the blood or by the liver schizonts when these enter the circulation, but the latter in their protected position in the parenchyma cells are unaffected. Therefore the merozoites released by the liver schizonts into the circulation are at once destroyed by the immune bodies, humoral or cellular or both, and so cannot attack the erythrocytes, while those which re-enter parenchyma cells are unaffected. If this immunity is lessened from any cause it is no longer effective in destroying the young merozoites escaping from the liver schizonts, and in consequence they succeed in invading the erythrocytes and so produce a parasitic relapse.

I shall now deal with pre-erythrocytic stages in human malaria.

Plasmodium vivax

In this case 2,010 mosquitoes infected with *P. vivax* were fed upon a human volunteer on two successive days. The volunteer was operated upon seven days later and a piece of liver removed. On examination this was found to contain schizonts of *P. vivax* very similar to those of *P. cynomolgi* found in the monkey. These schizonts measured up to 42 μ in diameter, and at 7 days old contained over 1,000 nuclei, so that the eventual number of merozoites produced was probably much greater. The description given of the schizonts of *P. cynomolgi* would apply generally to those of *P. vivax*. This experiment, where previously there had been doubts, proved conclusively the existence in vivax malaria of pre-erythrocytic forms, and there is no reason to doubt that here also there are later exo-erythrocytic forms which could produce relapses after recovery from the original attack of malaria.

Plasmodium falciparum

In this case there was no simian parasite readily available to guide one in devising experimental procedures, and so it was essential, from the beginning, to use a human volunteer in a transmission experiment.

A strain of *P. falciparum* was obtained from Rumania and used to infect *A. maculipennis* and *A. quadrimaculatus* mosquitoes. A total of 770 bites by heavily infected mosquitoes were inflicted on the human volunteer over a period of three successive days. Six days (140 hours) later a piece of liver was removed from the volunteer by open operation. If this should contain the expected pre-erythrocytic forms it would follow that the latter would be of three stages of development separated by 24-hour periods. On examining the biopsy specimen this prediction was proved to be correct and exo-erythrocytic stages were obtained of approximately six, five, and four days' development. Those of six days' development were fully developed schizonts with the merozoites already formed and ready to be released into the surrounding tissues. The forms of five and four days' development were schizonts, smaller in size and with the nuclei still in process of division preparatory to formation of merozoites. In the case of *P. falciparum* the fully developed schizonts were considerably larger than those of *P. cynomolgi*, measuring as they did 60 μ or more in diameter. They were less regular in shape than those of *P. cynomolgi* and tended to be multilobed. The merozoites were smaller and much more numerous.

Summary

It may be claimed that now, for the first time, unequivocal proof has been obtained that in simian and human malaria

pre-erythrocytic development of the parasites takes place in the parenchymal cells of the liver with the production of merozoites which invade the erythrocytes to establish the blood infection. At the same time strong evidence has been adduced to suggest that this developmental cycle in the liver persists after the establishment of the erythrocytic infection, may even exist without the latter, is relatively unaffected by the immunity response of the host, and is the probable source of relapses of the disease.

BIBLIOGRAPHY

Angelini, G. (1947). *Riv. Parasitt.*, **8**, 5.
Fairley, N. H. (1945). *Trans. R. Soc. trop. Med. Hyg.*, **38**, 311.
—— (1947). Ibid., **40**, 621.
Huff, C. G., and Coulston, F. (1944). *J. infect. Dis.*, **75**, 231.
James, S. P., and Tate, P. (1938). *Parasitology*, **30**, 128.
Mudrow, L. (1940). *Arch. Schiffs- u. Tropenhyg.*, **44**, 257.
Shortt, H. E., Fairley, N. H., Covell, G., Shute, P. G., and Garnham, P. C. C. (1949). *British Medical Journal*, **2**, 1006.
—— Garnham, P. C. C., Covell, G., and Shute, P. G. (1948). Ibid., **1**, 547.
—— Menon, K. P., and Iyer, P. V. S. (1940). *Indian J. med. Res.*, **28**, 273.

Medical Memoranda

Death from Atropine Poisoning

The following rare case is interesting enough to be placed on record.

CASE REPORT

A boy aged 2 years 9 months was brought to hospital on May 20, 1950, for the treatment of an alternating convergent squint which his mother had noticed five months previously. Atropine ointment 1% was prescribed and approximately 90 gr. (6 g.) was dispensed. The mother was given a glass rod with printed instructions about the method of administration.

The ointment was first used on May 23, when two applications were given, the first in the afternoon and the second in the evening. The mother stated that the application was made by first dipping the rod into the ointment, and that the amount applied was quite small. Next morning the child was not well and the parents called in their doctor, but a further application of the ointment was given. On the morning of May 25 the child had no breakfast, and at 9.15 a.m. he had a fit (tonic and clonic contractions) and was semiconscious afterwards. At 11 a.m. he had another fit, and was admitted to All Saints' Hospital, Chatham, at 2.20 p.m. under the care of Dr. Sadiq.

On admission his temperature was 97° F. (36.1° C.), pulse 120, and respirations 32. He was a well-nourished child. He had sordes on his lips; petechiae, mainly on the left side of the trunk; dilated pupils, not reacting to light; and slight opisthotonus. The cerebrospinal fluid was normal in every way. There was no growth of organisms from a throat swab. The white blood cells numbered 28,000 per c.mm. (polymorphs 72%, lymphocytes 23%, monocytes 5%). The blood sugar at 4 p.m. on the 25th was 30 mg. per 100 ml. Next day he had petechial haemorrhages on his neck, upper chest, elbows, and forearms, and a papular rash on his legs. His blood pressure was 130/60. His voice was hoarse; he cried without shedding tears and was restless. The blood urea was 60 mg. per 100 ml. He died at 9.45 p.m.

Post-mortem Examination.—This was carried out at 3.30 p.m. on May 27 by Dr. H. G. Close. The body was that of a well-nourished male child of stated age. The eyes were sunken and the pupils dilated. Bruises were found on the tip of the right iliac crest and below the left ankle. The air passages and lungs were dry. Several petechiae were present on the anterior aspect of the heart (weight 3 oz.—85 g.). There was a very small vegetation on the mitral valve. The thymus weighed 1 oz. (28 g.), the spleen 2 oz. (57 g.), and the lungs 9 oz. (255 g.). The liver (18 oz.—510 g.) was very pale, with several petechiae on the surface; microscopically, extensive fatty changes were seen. No gross abnormality was found in the kidneys (3 oz.—85 g.). The brain (44 oz.—1.25 kg.) was mushy, soft, and tore easily, and petechiae were present in the corpus callosum. The clinical story and post-mortem appearances are consistent with the diagnosis of atropine poisoning.

COMMENT

An analysis of the ointment showed that it contained 0.8% of atropine alkaloid, and the analyst stated that at least seven-eighths of the original quantity of the ointment dispensed was sent to him for analysis. Approximately ½ gr. (32 mg.) of ointment was picked up on the glass rod at each application. The total quantity administered, therefore, was approximately 3 gr. (0.2 g.), containing 1.6 mg. of alkaloid. The possibility that the child may have swallowed some of the ointment was considered, but almost all the ointment originally dispensed was accounted for.

Morton (1939) reported nine cases of atropine poisoning, two of which were fatal. In the first case six drops of 1% atropine solution were dropped into an injured eye, and after operation 1.5 g. of 1% atropine ointment was placed on the dressing next to the eye. Death occurred fourteen hours later. The total amount of atropine administered was 18.1 mg. In the second fatal case the pupils of both eyes were dilated with 1% atropine solution. Death occurred in under twenty-four hours and the total amount of atropine administered was 2 mg.

Hughes (1938) recorded a case, not fatal, in which 1% atropine ointment was smeared into both eyes twice daily for three days. On the third day the child was reported to be ill with a temperature, and the skin was flushed and very dry to the touch. Morphine and pilocarpine were given and recovery was uneventful.

My thanks are due to Dr. M. Sadiq for permission to publish this case and to Dr. H. G. Close for the pathological report.

W. E. HEATH, M.B., B.S., D.O.

REFERENCES

Hughes, C. A. (1938). *Trans. Ophthal. Soc. U.K.*, **58**, 444.
Morton, H. G. (1939). *J. Pediat.*, **14**, 755.

Neurological Complication After Combined Diphtheria and Pertussis Immunization

The occurrence of severe complications after an injection of pertussis vaccine is rare enough to merit record.

CASE REPORT

A girl aged 1 year was admitted to hospital on July 17, 1948, with left hemiplegia. She had been a healthy infant. There was no family or personal history of convulsions or allergy. Injections of diphtheria A.P.T. on May 9 and 19 had caused no apparent untoward effect. An injection of pertussis vaccine on June 17 similarly had caused no ill effect. On July 15 a mixture of alum-precipitated pertussis vaccine and diphtheria A.P.T. had been injected, and a few hours later she is said to have been quieter than usual, but by bedtime (about 17½ hours later) had become her usual self again. Early next morning she had been found in a fit with twitching of the face and both limbs on the left side, and 2½ gr. (0.16 g.) of phenobarbitone had been given. Shortly afterwards a state of semi-coma had ensued, lasting several hours, and later a left hemiplegia had developed.

On admission the child was very irritable, her temperature was 102° F. (38.9° C.). Physically she was well nourished. She had a left hemiplegia with little movement of the upper limb and none of the lower. The reflexes of the upper limb were absent, the knee-jerks were present and equal, but the left ankle-jerk was absent. The right plantar response was flexor but the left was indefinite. The abdominal reflexes were absent. There was no detectable involvement of the cranial nerves and the fundi oculorum were normal. The pyrexia subsided in two days.

On January 17 the spinal fluid was under normal pressure. It contained no excess of cells; 30 mg. of protein per 100 ml.; no excess of globulin; 730 mg. of chlorides per 100 ml. On January 20 a repeat tap showed that the fluid contained no excess of cells; 30 mg. of protein per 100 ml.; no excess of globulin; 720 mg. of chlorides per 100 ml.; 65 mg. of sugar. No organisms were grown. Queckenstedt's test was negative. The Wassermann reaction of the blood and spinal fluid was negative.

The hemiplegia improved rapidly, all the deep reflexes of the limbs and abdominal reflexes appearing within a week. The patient was discharged on July 31, a happy and lively baby with slight weakness of the affected limbs.

When seen again on August 5 there was no apparent weakness of the limbs. Her mother had noticed some clumsiness of the affected limbs in play, but considered that this was improving. There was no evidence of mental deficiency.

COMMENT

Anderson and Morris (1950) have reviewed the literature and reported a case which developed convulsions 36 hours after a first injection of combined diphtheria–pertussis antigen. Their case had had a previous history of convulsions.

The present case is of interest because no apparent ill-effects had been produced by previous injections of A.P.T. and alum-precipitated pertussis vaccine given singly; the convulsion followed the injection of a mixture of these two antigens, made by the same manufacturer. Sensitization as a result of the previous injections cannot be ruled out, but the frequency of allergic states and the rarity of serious neurological complications of this kind suggest that these reactions may have a genetic basis; a previous history of convulsions may therefore, pending further additions to our knowledge, be regarded as a contraindication to the use of pertussis antigens. It should not be forgotten that an attack of whooping-cough may cause encephalopathy with permanent residua, including mental changes (Levy and Perry, 1948).

J. VAHRMAN, M.B., B.S., C.P.H.,
Senior Registrar, Department of Infectious Diseases, Royal Free Hospital.

REFERENCES

Anderson, I. M., and Morris, D. (1950). *Lancet*, **1**, 537.
Levy, S., and Perry, H. A. (1948). *Amer. J. ment. Defic.*, **52**, 217.

An Emergency Leucotomy

Prefrontal leucotomy is now an established procedure in psychiatry. The indications for such an operation are usually regarded as certain forms of chronic mental illness which have not responded to more conservative methods. In the following case the operation may be correctly described as life-saving; and it would not be inaccurate to speak here of "an emergency leucotomy."

CASE REPORT

The patient, a woman aged 21, was admitted to hospital on August 6, 1947, with a provisional diagnosis of anorexia nervosa. She was the youngest child of a family of eight, whose father had committed suicide at the age of 54. Her childhood and adolescence had passed without revealing any abnormal personality traits. At 19 she became sensitive about her appearance and fastidious about her food, and developed the delusion that she was unable to swallow and that she might become "filled up with wind" and die. She would pretend to chew her food but secretly spit it out and hide it in odd corners. Her sleep was disturbed and she was losing weight. On admission her weight was 5 st. (31.8 kg.); two years previously it had been 7 st. (44.5 kg.). Apart from this peculiarity about eating, there were no other psychotic symptoms.

A course of modified insulin was given and strict hospital routine and observation were maintained. Her weight gradually returned to normal and she was discharged home on December 13 "happy, sociable, and eating and sleeping well."

After remaining well at home for four months her previous delusions and habits returned, and she was readmitted to hospital on June 30, 1948, in a dangerous state of emaciation. Her urine was loaded with acetone and her appearance was that of a concentration-camp victim. Her weight was 5 st. 5 lb. (34 kg.). She refused all food and required tube-feeding. Later, when her physical health was stronger, a course of E.C.T. was given. This treatment produced only very temporary remission, and within a few days of stopping it the refusal of food began again. Tube-feeding had to be resorted to. This was a painful procedure for all concerned, as the patient did all in her power to resist and to regurgitate the food. She made frequent promises to eat, but was a genius at deception. Food would be found hidden in the strangest places. She showed no insight into the danger she was in and could explain her refusal to eat only by saying "she came of a thin family."

A transorbital leucotomy was performed on December 6, 1948. This produced a temporary remission, but by March 13, 1949, she had returned to her previous state and tube-feeding had again to be resorted to.

It was at this stage that the emergency occurred. She developed a recurrent evening pyrexia. A radiograph of her chest showed "a cavity below the right clavicle with a little surrounding opacity, doubtless tuberculous." Her erythrocyte sedimentation rate at this date was 37 mm. in 1 hour. Further E.C.T. was now out of the question, and the prognosis was indeed grave. Her emaciated state and continued dependence on tube-feeding pointed to a fulminating phthisis soon ending the story.

A full leucotomy seemed now the only possible hope. This was performed on May 4. Convalescence was uneventful and she ate her food satisfactorily from that day forward. Before operation her weight was 5 st. 6 lb. (34.5 kg.) and a week after it was 5 st. 12 lb. (37.2 kg.). On June 27 it was 8 st. (50.8 kg.) and her erythrocyte sedimentation rate was 7 mm. in 1 hour.

In spite of the presence of a tuberculous cavity it was decided not to confine her to bed. The after-treatment of a leucotomized patient should be one of continued occupation, and this was considered a matter of priority in her case. Her activity was gradually increased and no rise of temperature was noticed. As the weeks passed her mental state improved concurrently with her physical condition. She became more interested in other people and in her own appearance, and her work at the occupational therapy class improved. On June 9 a further *x*-ray report read: "Cavity cleared below right clavicle and infection almost gone."

COMMENT

This case seems worthy of record for several reasons. (1) It raises an interesting point in psychiatric diagnosis. The initial symptoms were classically those of an anorexia nervosa, but the long duration of the illness, the temporary response to E.C.T., and the more permanent response to leucotomy suggest that basically the illness was schizophrenic. (2) It shows that when a transorbital leucotomy has proved a failure a full prefrontal operation may yet be a success. (3) The influence of the mental state on a patient suffering from phthisis is well known. In the above case a specifically psychiatric procedure and the ignoring of the physical disease during convalescence led to an eventual healing of a proved tubercular lesion—a healing as rapid as any collapse treatment would have produced.

My thanks are due to Dr. J. N. P. Moore, medical superintendent of St. Patrick's Hospital, Dublin, and to Professor A. McConnell and Mr. J. P. Lanigan, of the Neurosurgical Unit, St. Laurence's Hospital, Dublin, for their assistance with this case.

M. O'C. DRURY, M.D., D.P.M.,
Deputy Medical Superintendent, St. Patrick's Hospital, Dublin.

Reviews

POSTGRADUATE LECTURES

Postgraduate Obstetrics and Gynaecology. By F. J. Browne, M.D.(Aberd.), D.Sc., F.R.C.S.Ed., F.R.C.O.G. (Pp. 501; 107 figures. £2 10s., postage 1s. 6d. extra.) London: Butterworth and Co. 1950.

Professor F. J. Browne's energy and enthusiasm for teaching at all levels continue unbounded, to the admiration and envy of his friends and colleagues. Even since his nominal retirement a few years ago he has regularly conducted classes in advanced obstetrics and gynaecology for those seeking specialist rank and diplomas, helping by individual initiative to fill one of the gaps in the facilities for the training of such in this country.

The forty-five chapters in this book each represent the basis of one or other of his postgraduate lectures, selected to exclude so far as possible the material in his other book. They are mainly on those topics around which interest has centred in recent years, those which are likely "spots" for any higher examination, and those on which anyone engaged in practice or teaching may wish to have a clear and concise statement of the latest views. The outlook throughout is academic rather than practical, some of the chapters being good, some less good, but all useful. In his introduction Professor Browne writes: "The aim of a teacher should be, I think, to know the literature as far as he can, to filter it through his mind and give his conclusions, right or wrong." Not everyone will agree with this when the result is a predigested meal which satisfies rather than stimulates the appetite and deprives the student of the necessity to think and to browse among journals. Nevertheless, there is no doubt that postgraduate students will welcome it, and in doing so should beware lest it result in a uniformity in replies to examination questions. The examiners also can hardly fail to have read it, and, human nature being as it is, may grow weary of script after script containing thinly veiled chapter "X" of F. J. Browne.

T. N. A. JEFFCOATE.

CLASSIFICATION OF SHIGELLAE

On the Classification of the Shigella Types. With special reference to the Flexner Group. By Sten Madsen. (Pp. 122. No price.) Copenhagen: Ejnar Munksgaard. 1949.

Those bacteriologists working on the identification and the preparation of diagnostic sera for the investigation of organisms of the genus *Shigella* will be grateful to the author for collecting all the more important findings in his book. Madsen obained 230 strains of dysentery bacilli, mainly from British and American sources, but also from Denmark and other parts of the world, including strains used in earlier classifications. Using these, he confirms the use of the biochemical division into mannitol-fermenting and non-fermenting groups. The former group consists of *Sh. flexneri* types 1–6, *Sh. boydii* types 1–7, and *Sh. sonnei*; the latter of *Sh. shigae, Sh. schmitzii,* and *Sh. large-sachsii* types 1–5. He replaces with arabic the roman numerals commonly used in recent classifications. The organisms "alkalescens" and "dispar" are excluded from this genus on serological grounds, which suggest that they are more closely related to the genus *Escherichia.* Many observers will agree with this exclusion, since the organisms do not cause clinical dysentery. Details are given of both the typical and atypical biochemical reactions of all strains studied. In the chapter on serology the author describes the preparation of sera as well as his method of absorption used in the preparation of type-specific sera. His work on the Flexner group shows that he did not find one group antigen common to all types 1–6; in this respect his findings differ from those of some other investigators.

This monograph, the result of much careful work, is another step towards obtaining an internationally acceptable stable scheme for the classification of the shigella group. The descriptions of media, technique, and detailed laboratory findings will be of great assistance in the routine laboratory, but particularly in the specialized laboratory concerned with the full identification of strains.

JOAN TAYLOR.

THE STATISTICIAN'S JOB

Practical Statistics in Health and Medical Work. By Ruth Rice Puffer, Dr.P.H. (Pp. 238. £1 12s.) London: McGraw-Hill Publishing Co. 1950.

This book is an expansion of lectures given by the author to the School of Public Health of the University of Chile in 1946. The subject has been liberally illustrated with examples from the work of the Tennessee Department of Health, where Dr. Puffer has been Director of Statistical Service since 1933. Much of the advice she gives is no wishful idealism but the keynote of her work. She preaches what she practises—that careful planning is the key to the successful solution of any problem in field work, and that the statistician's job is to help design the experiment, not merely to analyse data for which he has not been responsible. She emphasizes that a knowledge of the field of study is more important than elaborate analysis, and that for many problems simple statistical techniques are sufficient.

The first four chapters of the book are on the general principles covering the uses of statistics in public health work, planning of studies, and presentation of data. Much of this could well be condensed, while Chapter 5, "Elementary Statistical Method," is at once too short for beginners and unnecessary for those with any previous knowledge. It is in the succeeding chapters, where she draws on her own experience, that the book is valuable. For the English reader the discussion of secondary attack rates, and the need for defining what Frost called the "index case," is useful. In two chapters she considers person-years as a measure of exposure to risk and life-table techniques in long-term and follow-up studies, uses which in the future will probably be of great importance. The sections on morbidity surveys in the U.S.A. make clear the distinction between prevalence and incidence data. A large part of the chapter on industrial mortality and morbidity is drawn from English data.

There are omissions, among the more important of which are a discussion of the uses and difficulties of sampling in field studies, but the student wishing to solve an epidemiological problem will find useful advice in this book.

J. KNOWELDEN.

OCCUPATIONAL THERAPY

Occupational Therapy; Principles and Practice. Edited by W. R. Dunton, jun., M.D., and S. Licht, M.D. (Pp. 321; 12 illustrations. £2 5s.) Oxford: Blackwell Scientific Publications.

Although occupational therapy has been in use as a form of hospital treatment for nearly forty years, particularly in mental hospitals and tuberculosis sanatoria, little was written on the subject before the second world war. It was then that the value of this type of therapy came to be more fully recognized and understood, not merely for its

use in providing a pleasant diversion from brooding over disabilities and apprehensions, but as a positive means of restoring muscular tone, stimulating interest in creative work and providing recuperative activity for both body and mind.

This volume is the work of the associate editors of the useful bi-monthly journal *Occupational Therapy and Rehabilitation*, and, unlike previous treatises on the subject, is primarily intended for physicians. It has been written with the purpose of acquainting them with the varied conditions in which occupational therapy can make a direct contribution to ordinary medical and surgical treatment. That is why it probably includes many details of purely pathological and diagnostic interest which appear somewhat irrelevant in a book of this nature, and which tend to obscure the main object of the work.

Among interesting subjects discussed at length by expert contributors are the various purposes served by occupational therapy in the treatment of psychiatric disorders; kinesiology, and its value in selecting suitable handicrafts for weakened muscles; the place of drama therapy, and its psychotherapeutic function; and the type of occupational methods most suitable in the rehabilitation of cases of pulmonary tuberculosis, heart disease, and cerebral diplegia. Miss Lyttleton (a British occupational therapist) contributes a useful chapter on the treatment of amputees, with valuable hints on the right psychological approach.

The actual technique of occupational therapy is very scantily described, and there is but little reference to the details of application in traumatic and orthopaedic cases, or to the adaptation of machines in industry itself for the rehabilitation of injured workmen—such as is proving so fruitful a development of occupational therapy in Britain. The book will, however, give the general physician a wide view of the varied possibilities of this form of hospital treatment.

HAROLD BALME.

FOOT DISORDERS

The Practice of Chiropody. By Keith Campbell Jones. Foreword by Norman C. Lake, M.D., M.S., D.Sc., F.R.C.S. (Pp. 279; illustrated. £2 2s.) Sydney and London: Angus and Robertson, 48, Bloomsbury Street, W.C.1.

This is an excellent straightforward textbook for the student and practitioner of chiropody. The author is a past president and foundation member of the Australasian Guild of Chiropodists, and for many years has been recognized as one of the foremost teachers in his profession. His experience as editor of a journal devoted to chiropody has enabled him to present the material in a readable yet concise form.

He covers the subject comprehensively and discusses the various problems with admirable common sense. He gives in full the prescriptions of all therapeutic preparations in ordinary use, and includes a useful account of chiropodial physiotherapy. The chapters on the organization and conduct of a modern practice, on military chiropody, and on the problems of post-war chiropody are noteworthy. The only illustrations are of anatomical drawings of the leg and foot. These, though good in themselves, lose much of their value by being scattered haphazardly throughout the book. It is to be hoped that in future editions the illustrations will be grouped together in close relationship to the relevant text. The production is otherwise good, though the price seems rather high for a book so sparsely illustrated and printed on paper of only moderate quality.

J. C. ADAMS.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

The Physiological Basis of Medical Practice. By C. H. Best, C.B.E., M.A., M.D., D.Sc., F.R.S., F.R.C.P.Can., and N. B. Taylor, V.D., M.D., F.R.S.Can., F.R.C.S.Ed., F.R.C.P.Can., M.R.C.S., L.R.C.P. 5th ed. (Pp. 1,330. 84s.) London: Baillière, Tindall and Cox. 1950.

Worth and Chavasse's Squint: The Binocular Reflexes and the Treatment of Strabismus. By T. K. Lyle, C.B.E., M.A., M.D., M.Chir., M.R.C.P., F.R.C.S. 8th ed. (Pp. 319. 35s.) London: Baillière, Tindall and Cox. 1950.

Essays in Zen Buddhism (Second Series). By D. T. Suzuki, D.Litt. (Pp. 348. 15s.) London: Rider. 1950.

The Medical Annual, 1950. Edited by Sir H. Tidy, K.B.E., M.A., M.D., F.R.C.P., and A. Rendle Short, M.D., B.S., B.Sc., F.R.C.S. (Pp. 448. 25s.) Bristol: John Wright. London: Simpkin Marshall. 1950.

Ionization Chambers and Counters. By D. H. Wilkinson, M.A., Ph.D. (Pp. 266. 25s.) Cambridge: University Press. 1950

Thorpe's Dictionary of Applied Chemistry. 4th ed. Vol. 10. (Pp. 913. 100s.) London: Longmans, Green. 1950.

Clinical Orthoptic Procedure. By W. Smith, O.D. (Pp. 393. 56s.) London: Henry Kimpton. 1950.

Collected Papers of the Mayo Clinic and the Mayo Foundation. Edited by R. M. Hewitt, B.A., M.A., M.D., and others. Vol. 41. (Pp. 820. 52s. 6d.) London: Saunders. 1950.

Parenthood. By C. M. Owen, S.R.N. (Pp. 192. 7s. 6d.) London: William Heinemann. 1950.

A Doctor Remembers. By E. A. Barton. 2nd ed. (Pp. 288. 12s. 6d.) London: Seeley, Service. 1950.

Introduction to Motherhood. By G. D. Read, M.A., M.D. (Pp. 92. 6s.) London: William Heinemann. 1950.

A Measuring Diagram for Daylight Illumination. By P. J. Waldram, F.R.I.C.S. (Pp. 19. 5s.) London: Batsford. 1950.

Papers of the Michigan Academy of Science, Arts and Letters. Edited by E. S. McCartney and F. K. Sparrow. Vol. 34 (1948). (Pp. 355. 55s.) London: Geoffrey Cumberlege, Oxford University Press. 1950.

Ophthalmic Operations. By S. Philps, F.R.C.S. (Pp. 397. 50s.) London: Baillière, Tindall and Cox. 1950.

Help for Childless Couples. Marriage Guidance Booklets—No. 4. (Pp. 23. 6d.) London: National Marriage Guidance Council. 1950.

Williams Obstetrics. By N. J. Eastman. 10th ed. (Pp. 1,176. No price.) New York: Appleton-Century-Crofts. 1950.

Physician's Handbook. By M. A. Krupp, M.D., and others. 6th ed. (Pp. 380. $2.50.) Palo Alto, Cal.: University Medical Publishers. 1950.

German Aviation Medicine, World War 2. Vols. 1 and 2. Edited by the Surgeon-General, U.S. Air Force. (Pp. 1,302. $8.50 the set: in buckram $4.25.) Washington 25, D.C.: Department of the Air Force. 1950.

Spaltlampen-Mikroskopie des hinteren Augenabschnittes. By K. Hruby. (Pp. 164. M. 28.60.) Vienna and Innsbruck: Urban and Schwarzenberg. 1950.

Segment-Therapie. By M. Kibler. (Pp. 136. M. 9.50.) Stuttgart: Marquardt. 1950.

Leitfaden für Prostatiker. By J. Minder, M.D. (Pp. 68. M. 4.80.) Stuttgart: Georg Thieme. 1950.

Die Lunge des Kindes. By S. Engel. (Pp. 288. M. 29.70.) Stuttgart: Georg Thieme. 1950.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY SEPTEMBER 9 1950

INTERNATIONAL CONGRESS OF INTERNAL MEDICINE

Two years ago a group of physicians met in Basle to found the International Society of Internal Medicine. The first Congress of the Society will be held in Paris next week under the presidency of Professor André Lemierre, and it is expected that between 1,000 and 1,500 delegates from all over the world will be present. It is unfortunate that there is no representative of the U.S.S.R. on the International Committee of the Society, the existence of which owes much to the inspiration of Professor A. Gigon, of Switzerland.

As the Congress has limited funds at its disposal those responsible for its organization asked certain internationally known periodicals to publish some of the principal contributions to be read next week. This task has been shared by the *Acta Medica Scandinavica*, the *Schweizerische Medizinische Wochenschrift*, the *Semaine des Hôpitaux*, and the *British Medical Journal*. In the opening pages of this week's issue are printed papers whose excellence is a testimony to the wisdom of those who, under the guidance of the Secretary-General of the Congress, Professor L. Justin-Besançon, of Paris, chose the subjects and speakers for next week's meeting. Copies of the journals participating in this novel method of publishing part of the proceedings of a congress will be in the hands of all those who attend it on Monday, September 11. This *Journal* welcomes the opportunity of making this small contribution to international medicine.

PERNICIOUS ANAEMIA AND THE INTRINSIC FACTOR

An important concomitant of two great chemical discoveries—the isolation[1] and synthesis of pteroylglutamic acid (folic acid) and the isolation[2] of vitamin B_{12}—is the evidence that these substances are factors essential not only for the maintenance of normal haematopoiesis but are also required for the growth of many kinds of living cells and organisms. In the study of pernicious anaemia, however, the nature of the gastric lesion still remains an unsolved problem. It is now apparent that pteroylglutamic acid is not the extrinsic factor of Castle. Though effective in securing normoblastic transformation of the megaloblastic marrow in pernicious anaemia, it does not halt the onset of subacute combined degeneration and may indeed precipitate it. There is some evidence that it may also fail to maintain adequate numbers of erythrocytes in the circulation. On the other hand, the effect of injections of vitamin B_{12} on both the haematopoietic and central nervous systems more closely resembles that of adequate parenteral liver therapy. Pteroylglutamic acid is as effective by the oral as by the parenteral route in procuring haematopoietic response, but vitamin B_{12} is very variable in its effects when given by mouth, and, at best, far larger doses are required than by injection to produce comparable results. All this recent work links up with the fundamental research of Castle and his co-workers on the intrinsic factor, for when vitamin B_{12} together with normal gastric juice is given to patients with pernicious anaemia the haematopoietic response is good.[3,4] In the opening pages of this issue Dr. Byron E. Hall describes experiments which shed light on the probable relationship of vitamin B_{12} to the intrinsic factor.

Both the nature and the mode of action of the intrinsic factor are mysterious. It has been established that in normal gastric juice it is heat labile, it is separable from pepsin, and it will not pass through semipermeable membranes. The effectiveness of dry preparations of hog stomach when given orally in pernicious anaemia may be explained by their content of both vitamin B_{12} and intrinsic factor.[5] Dr. Hall, collaborating with Dr. Bethell and his associates, has found that lyophilized extracts of gastric and duodenal mucosa of swine are particularly effective in promoting response to orally administered vitamin B_{12} in pernicious anaemia. Interaction between vitamin B_{12} and the intrinsic factor appears necessary for the absorption of the former from the human alimentary tract, but the nature of the reaction and its specificity and function are still under investigation. Some workers have suggested that the intrinsic factor has an enzymatic function, possibly acting on peptide linkages. Dr. Hall also supports the concept of an enzymatic action. Simple liberation of vitamin B_{12} from combined forms in the diet appears unlikely from the results obtained by giving the free vitamin and intrinsic factor preparations together by mouth. Although much is now known of the chemistry of the vitamin B_{12} molecule, including evidence for the presence of the

[1] Pfiffner, J. J., *et al.*, *Science*, 1943, **97**, 404.
[2] Smith, E. L., *Nature, Lond.*, 1948, **161**, 638.
[3] Berk, L., Castle, W. B., *et al.*, *New Engl. J. Med.*, 1948, **239**, 911.
[4] Hall, B. E., Morgan, E. H., and Campbell, D. C., *Proc. Mayo Clin.*, 1949, **24**, 99.
[5] Bethell, F. H., *et al.*, *Univ. Hosp. Bull. Ann Arbor*, 1949, **15**, 49.
[6] Brink, N. G., and Folkers, K., *J. Amer. chem. Soc.*, 1949, **71**, 2951.
[7] Beaven, G. R., *et al.*, *J. Pharm. Pharmacol.*, 1949, **1**, 957.
[8] *Proc. Soc. exp. Biol. Med.*, 1950, **73**, 15.
[9] *J. Amer. chem. Soc.*, 1949, **71**, 3858.
[10] Meyer, C. E., Eppstein, S. H., Bethell, F. H., and Hall, B. E., *Fed. Proc.*, 1950, **9**, 205.
[11] *British Medical Journal*, 1949, **2**, 731.
[12] *Blood*, 1949, **4**, 793 and 803.
[13] *J. Path. Bact.*, 1928, **31**, 557.

benziminazole nucleus,[6 7] there is no proof that any chemical modification is brought about by the intrinsic factor. The possibility of small structural changes not reflected by such physical properties as the absorption spectrum is admitted by Wolf and his colleagues,[8] but these workers also found no change in the microbiological activity of vitamin B_{12} for *L. lactis* Dorner when added to normal human gastric juice at *p*H 2, 3, and 7 and incubated for periods up to 22 hours at 28–30° C.

Evidence that "binding" of vitamin B_{12} occurs in certain conditions may have an important bearing on the problem of utilization. Ternberg and Eakin[9] have reported that the non-dialysable, heat-labile component of normal gastric juice unites with vitamin B_{12} and renders it non-available to such bacteria as *Bact. coli*, *L. lactis* Dorner, and *L. leichmannii*, and that heating liberates the microbiologically active vitamin B_{12} again from this complex. These authors have named the heat-labile component of the gastric juice "apoerythein." This is less abundant than normal in the gastric juice of patients with pernicious anaemia, and it is suggested that the substance is related to or identical with the intrinsic factor. Dr. Hall reports that the duodenal mucosal extracts of hogs which potentiated the absorption of vitamin B_{12} were also active in rendering vitamin B_{12} non-available to *L. leichmannii*. There is evidence that egg-white lysozyme will unite with vitamin B_{12} to form a complex non-available to *L. lactis* Dorner.[10] This complex is ineffective haematopoietically when given by mouth, and Dr. Hall has also discovered extracts of swine gastric mucosa with strong binding capacity for vitamin B_{12}, but not very effective clinically.

This evidence suggests that, although vitamin B_{12} may interact with several substances and lose microbiological activity, it is only after interaction with the intrinsic factor that increased absorption from the human alimentary tract takes place. How does this tally with the available evidence on the aetiology of pernicious anaemia? The simplest view is that grossly reduced production of intrinsic factor in pernicious anaemia is a consequence of atrophic gastritis and that vitamin B_{12} in food fails to be modified and absorbed. But the question of why absorption fails remains. The intrinsic factor may act in several ways—by aiding the passage of vitamin B_{12} through the intestinal mucosa, by protecting it from destruction within the lumen, or by preventing its assimilation by micro-organisms growing in the intestinal tract—but, as Dr. Hall points out, there is little direct evidence to support any of these theories. The possible role of micro-organisms in the development of the megaloblastic change in pernicious anaemia is interesting, in view of Frazer's[11] remarks about the importance of intestinal bacterial competition in the sprue syndrome and the work of Cameron, Watson, and Witts[12] on macrocytic anaemia occurring in association with anastomoses and strictures of the intestine. A similar anaemia can also be produced experimentally in rats. Davidson[13] showed, over 20 years ago, that the faecal population of micro-organisms may be abnormally large in pernicious anaemia. Gastric atrophy and failure of secretion may be the cause of this, so that the lack of intrinsic factor still remains the central problem. Whether the gastric atrophy is the primary lesion or only part of a widespread tissue defect, and the extent to which the process is genetically conditioned, are questions which cannot yet be answered with assurance.

KITCHEN HYGIENE

Over 6,000 cases of food-poisoning were notified last year, and no doubt a great many more went unrecorded. Slovenly handling of food is not only aesthetically unpleasant: it is a positive danger to health—the more so since eating in canteens and publicly owned restaurants became common. It is surprising that public opinion has not reacted more vigorously to some of the revelations about dirty food which have appeared in the newspapers, but the Ministry of Health and some local authorities are striving to bring the important points home to the professional food-handler and the housewife, and the Ministry of Food has sent to local authorities model by-laws[1] which will enable them to secure "the observance of sanitary and cleanly conditions and practices in connexion with the handling, wrapping, and delivery of food." At the British Food Fair which has been held at Olympia during the last fortnight the Ministry of Health's portable exhibition has been on view. This can be lent to local authorities to support their clean-food campaigns. At the same Fair the Central Council for Health Education convened a conference on the subject of food and drink infections, and it can only be hoped that as a result of all these efforts the public will demand that the high standard set by some food manufacturers and caterers will soon be followed by all.

It is impossible to lay down definite standards to which all kitchens must conform, for conditions differ greatly even among those preparing communal meals. The aim is to ensure that in the storage, preparation, and serving of food no deleterious bacteria are added and no opportunities are allowed for bacterial multiplication to occur. To secure this there must be a high standard of personal hygiene among the staff handling the food,

[1] Model Byelaws: Series 1, 1949, H.M.S.O., London.
[2] *Mon. Bull. Min. Hlth*, 1950, **9**, 22.
[3] Ibid., 1950, **9**, 38.
[4] *J. Hyg., Camb.*, 1947, **45**, 151.
[5] *Hygienic Food Handling*, published by Marks & Spencer, Ltd., 1949.
[6] *Med. Offr*, 1949, **82**, 257.

scrupulous cleanliness of kitchen and dining-room utensils, and adequate cold-storage space. Large numbers of organisms, including potential pathogens, have often been found in bacteriological investigations of kitchen utensils, and Frisby[2] has recently compared the results obtained when washing-up with soda and with a proprietary cleansing agent containing hypochlorite and a detergent. Sinks were redosed every 15 minutes and emptied and refilled every 30 minutes. With soda, bacterial plate counts per utensil were in the hundreds and occasionally in the thousands; bacteria in the washing-up water were uncountable even at a dilution of 10^{-4}; and the sinks even after cleaning yielded very high bacterial counts, faecal coli being among the organisms grown. The temperature of washing-up waters sampled at the height of the lunch-time rush in a busy canteen never exceeded 52° C. When the proprietary cleanser was used the bacterial count was usually below 100 per utensil, and some were sterile. The washing-up water and the sinks were almost sterile. Poor-quality cutlery deteriorated in the presence of hypochlorite and eventually had to be washed in the detergent only. Redosing with detergent had to be accurately timed: if the intervals rose to 20 minutes free chlorine disappeared from the water and the bactericidal power was lost. Higgins and Hobbs[3] inspected the kitchens of 30 catering establishments classified according to the washing and rinsing equipment provided, and investigated the number and type of bacteria remaining on utensils after washing. In one-sink kitchens high bacterial counts were obtained, but these were reduced if utensils were rinsed under running hot water and drained (not wiped) dry. The results obtained in two-sink kitchens (washing and rinsing) were only slightly better, probably owing to the low temperature of the rinse water. The third group—two sinks, one of which was "sterilizing," with the water thermostatically maintained at a constant temperature—was more satisfactory: plates washed by hand in water containing soap, soda, or synthetic detergent and chloramine compound were placed in metal racks and immersed for half a minute in the rinse water maintained at 170°–180° F. (76.6°–82.2° C.), and they were then stood in a hot-plate container without drying. Of articles washed in this way 63% attained the United States Public Health Service standard of fewer than 100 organisms per utensil, and intestinal and respiratory organisms were absent. In a fourth group of kitchens (with mechanical dish-washing machines) bacterial counts were much higher, probably due to lack of care in the supervision of the machine. Rinse waters were generally below the recommended temperature, necessitating hand drying, with the consequent addition of organisms from the cloth.

These investigations suggest that an efficient and simple method of cleansing tableware is washing with a detergent and rinsing at a temperature high enough to sterilize. This obviates the use of dish-cloths, for the utensils will dry in the air. Knox and Walker[4] investigated the washing and sterilization of food containers from a central kitchen supplying 3,000 meals a day, and they found that bacteriologically good results could be obtained with two sinks, one containing plenty of hot soapy water with soda and the other rinsing water at 80° C. After rinsing, the utensils dried in the air without the need for wiping. This method does not need much expert supervision and could be adopted by the least pretentious of feeding-places.

A more difficult problem is the personal hygiene of the food-handler. In larger kitchens, such as those of catering establishments and industrial works, with modern equipment and superintendents alive to the possibility of infection, personal cleanliness and a planned hygienic routine can be enforced and a high standard maintained. Such a routine has been well described in an excellent booklet published by one large company.[5] Food-handlers are medically examined before engagement and are periodically re-examined. Diarrhoea, severe colds, and septic skin infections must be reported, and the affected workers are temporarily withdrawn from their work. The harm which can be done by, say, a cook with a septic hand was well shown by Drs. E. L. M. Millar and M. Pownall in a paper which appeared in last week's *Journal*. It is much more difficult to maintain a high standard of personal hygiene in the small kitchens of private hotels, cafés, and snack-bars. The premises are often antiquated, with insufficient or no wash-basins and water-closets for the staff and equally unsatisfactory washing facilities for the dishes. The staff may be inadequate in number and poor in quality. No two premises are alike and no two sets of problems identical, and local authorities may find it good policy to appoint a keen sanitary inspector as food hygiene officer, with the sole task of improving standards of cleanliness. Such a person, with tact and patience, can suggest the most suitable methods for each kitchen, and by routine visits can keep alight any spark of enthusiasm that the staff may have shown. By regular sampling of utensils and washing-waters he can keep a check on method and supply a standard at which to aim. It is theoretically desirable that catarrhal and intestinal illness in food-handlers should be notified and that nasal and faecal specimens should be bacteriologically examined before the returned worker is allowed to handle food, but at present this is impracticable. A good sanitary inspector, however, can often obtain such specimens voluntarily. Bousfield[5] has suggested that, if we require food-handlers to have higher standards of personal hygiene, then the work of education must be started now in the schools. Perhaps it is too much to hope that education in the home could be equally effective.

NEOMYCIN

The list of antibiotics now known to have an action on the tubercle bacillus and presented by Dr. S. A. Waksman in a paper appearing in this issue is a formidable one: the majority are of course unsuitable for therapeutic use, usually on account of toxicity if for no other reason. It will not be forgotten in Paris, where Dr. Waksman is reading his paper at the First International Congress of Internal Medicine, that the first recorded use of a fungus product for treating tuberculosis was made in that city: Vaudremer treated 200 cases with an extract of *Aspergillus fumigatus* some 40 years ago. Waksman naturally deals mainly with streptomycin, not only giving a concise account of its remarkable achievements based on the well-known findings of American and British studies but emphasizing its two main drawbacks. These are the toxic effects of larger doses on the eighth nerve and the capacity of tubercle bacilli to acquire a high degree of resistance to the drug, which, once acquired, is permanent. These imperfections demand that if possible other antibiotics should be identified which can supplement its action or if necessary replace it, and it is suggested in this paper that such an antibiotic may have been found in neomycin.

The discovery of neomycin was announced by Waksman and Lechevalier[1] little more than a year ago. It is another product of the indefatigable search among the soil actinomycetes for useful producers of antibiotic substances—a search which has given us not only streptomycin but aureomycin, chloromycetin, and terramycin. Its source is *Streptomyces fradiae*, which is also reported by Swart, Romano, and Waksman[2] to form another substance, fradicin, which has no action on bacteria but is highly active against many species of fungi. Neomycin has a wide range of activity, most marked against Gram-negative bacilli and mycobacteriae. In the treatment of infections in mice due to the former, exemplified by *Salm. paratyphi B* and *Salm. pullorum*, Waksman and his colleagues[3] showed it to be more effective than streptomycin, and in another paper they have given particulars of its action on 52 species.[4] Organisms in the genera *Mycobacterium* and *Bacillus* and those of the enteric and dysentery groups are in general very susceptible, as are some other but not all species of Gram-negative bacilli: some streptococci, the pneumococcus, and *Cl. welchii* are much more resistant. Warth, Chandler, and Bliss[5] found it active *in vivo* as well as *in vitro* against *Bact. friedländeri* and *H. influenzae* and without effect on streptococcal and pneumococcal infections. They emphasize its high *in vitro* activity against both *Proteus* and *Pseudomonas* (presumably *Ps. pyocyanea*), characterizing it as the only substance known to them which attacks both of these organisms. This last interesting finding is to a large extent confirmed in the studies of Waisbren and Spink,[6] who nevertheless found that among their numerous strains some showed varying degrees of resistance.

This is the general picture of the potentialities of neomycin, but two important facts remain to be added which are of particular interest if it is to be used in the treatment of tuberculosis. One is that organisms which have become resistant to streptomycin remain sensitive to neomycin. Secondly, although some bacterial resistance to neomycin can be acquired, the process is a slow and gradual one. Waisbren and Spink have induced resistance to neomycin by the usual procedures and point out that it is of the "penicillin" and not the "streptomycin" type. Weiss and Waksman[7] also found that organisms rendered resistant to neomycin had an impaired vitality and growth rate and lost their resistance on transfer to normal medium. All these facts are encouraging, but it still appears uncertain whether neomycin will find a place in the treatment of tuberculosis or indeed of any other condition, because its toxicity has apparently yet to be fully ascertained. The only reports on this, so far as we are aware, refer to acute toxicity tests in mice: it seems that different batches have varied in their effects, some of the latter being lethal in lower doses than the original product.[4] These studies will have to be extended to other animals. Waksman mentions that the drug has actually been given to certain cases of human tuberculosis with good results, and with possible temporary toxic effects, presumably referable to the kidneys in two of the cases. Pending further information on this aspect of the action of neomycin its therapeutic usefulness must evidently remain *sub judice*.

1 *Science*, 1949, **109**, 305.
2 *Proc. Soc. exp. Biol., N.Y.*, 1950, **73**, 376.
3 *J. Bact.*, 1949, **58**, 229.
4 Waksman, S. A., Katz, E., and Lechevalier, H., *J. Lab. clin. Med.*, 1950, **36**, 93.
5 *Bull. Johns Hopk. Hosp.*, 1950, **86**, 169.
6 *Proc. Soc. exp. Biol., N.Y.*, 1950, **74**, 35.
7 *Proc. nat. Acad. Sci., Wash.*, 1950, **36**, 293.

ELECTRON STERILIZATION

The attraction of sterilizing food by electrons or *x* radiation is that penetration is virtually instantaneous up to the limit of depth which can be usefully reached. The possibilities have lately been examined at the Massachusetts Institute of Technology, and Brasch and Huber[1] have described a machine designed for practical use to which the name "capacitron" has been given. The proposed method is similar in conception to the *x*-ray treatment of cancer: the aim in each case is to render the cells irradiated incapable of division. With mammalian cells there is evidence that vulnerability is limited to the division process, and it is supposed that it is because of their greater rate of proliferation that cancer cells suffer the greater damage. With bacterial cells the evidence is that they can be rendered incapable of division at any time; and, provided that the initial count is not too high, it should be possible to achieve a 100% kill in a single short irradiation of high dosage. In their examination of the physical possibilities of this method Trump and Van de Graaff[2] pointed out that electron irradiation is much more efficient than the *x*-ray method. As against this, the penetration depth is less starting with electrons than starting with *x* rays: a fat herring might have to be irradiated from both sides for sterilization to be effective. Dunn and his colleagues[3] have studied the effects of electron sterilization on heat-resistant Gram-positive and Gram-negative bacteria, on

1 *Science*, 1947, **105**, 112.
2 *J app. Phys.*, 1949, **19**, 599.
3 Ibid., 1949, **19**, 605.
4 *Nucleonics*, 1949, Vol. 5, No. 2, p. 50.

spore-forming and non-spore-forming bacteria, on moulds, and on some foods. Doses of 500,000 roentgens usually destroyed all non-spore-forming bacteria and 99.9% of the spore-formers, while 1,000,000 roentgens rendered apple juice 99.999% sterile. The effect is cumulative: each increment of dose destroys the same proportion of bacteria, and if the dose is big enough in relation to the initial bacterial count not a single cell will survive. In the equipment which has been developed at the Institute irradiation is with 3,000,000 volts electrons, and sterilization is effected in pulses of one-millionth-second duration produced at about one-second intervals. It could therefore be a moving-belt process, but careful design would be needed. Trump and Van de Graaff state that "high energy cathode rays and *x* rays offer a new and effective means of producing biological, bacteriological, and even chemical changes on a practical scale." Stern and his colleagues suggest on slender evidence that the changes in bacteria which render them incapable of division can be regarded as being of a different kind from the disruption of normal chemical molecules and that effects "on the taste, odour, and appearance" of food need not be feared. On the other hand, Dunn and his colleagues found that the colour of butter was progressively destroyed, and Goldblith and Proctor[4] have shown a reduction in riboflavin and carotene, which in the case of the latter amounted to an 80% loss under some conditions. These aspects of the matter are now being further investigated by the Department of Scientific and Industrial Research at the Low Temperature Research Station, Cambridge: they are the equivalent, in this new method of food treatment, to the effects of *x* radiation on normal cells in the treatment of cancer.

MEDICAL BIBLIOGRAPHY

The recent decision to discontinue the *Index Catalogue of the Library of the Surgeon-General's Office* (Army Medical Library, Washington) is a serious loss to medical bibliography. Since 1927 the *Index Catalogue* has been supplemented by the more up-to-date *Quarterly Cumulative Index Medicus*, published by the American Medical Association. In its early days the latter made available an author-subject index of books and papers within three months of their publication, but it has for some years become progressively more out of date, and at present is over eighteen months late. Nevertheless it has always been accurately and skilfully edited. During the last war the necessity for a really up-to-date index of medical literature resulted in the publication of the weekly *Current List of Medical Literature*, which, although more difficult to consult and less well produced, provided an index which could properly be called current. Responsibility for its production was soon taken over by the Army Medical Library. It has, however, slowly fallen behind, and in June there was a "back log" of about four months. The decease of the *Index Catalogue* and the lateness of the *Index Medicus* have led to the decision to improve the *Current List* and to publish it monthly.

The first issue of the *Current List* in its new form, dated July, 1950, has now reached this country. It is not yet as up to date as might be hoped; for example, the issues of the *British Medical Journal* and *Lancet* for April 15 appear in it, but no doubt it will eventually absorb the accumulation left by its weekly predecessor. It includes an alphabetical list of over 1,300 journals regularly indexed as received, a list of contents of each journal received during the month (arranged alphabetically by title of journal), and a combined author and subject index. Annual indexes will also be published. The July issue lists 2,992 items. All articles in a given journal are indexed, and titles of articles in foreign languages are followed by an English translation. New titles will be added gradually to the list of journals covered. The *Current List* will not displace the *Quarterly Cumulative Index Medicus*; it will provide a more up-to-date index of current medical literature, although it will not be quite so easy to use as the latter. It is reproduced by photo-offset; subscription outside the U.S.A. is $11.50 per annum. The number of journals indexed by the *Current List* will probably increase rapidly, and it should become one of the most important bibliographical aids in medicine. It might increase the usefulness of the publication if lists of medical books were included.

LINEAR ACCELERATORS

The Ministry of Health with the Department of Health for Scotland have recently placed orders for five new 4,000,000-volt "linear accelerators" for the treatment of malignant disease. One of these is going to Scotland, one to London, and three to the provinces as a first step in the equipment of some of the larger radiotherapy centres with high-voltage apparatus of British design, material, and craftsmanship. Since the war higher voltage apparatus has come steadily into wider use in radiotherapy departments all over the world, and the linear accelerator is one of the major British contributions to this advance. In 1945 experimental work at the Atomic Energy Research Establishment, Malvern, under Mr. D. W. Fry, led to the development of the apparatus which has now been ordered. The first 4,000,000-volt machine of this type was operated successfully in February, 1948. The apparatus employs high-power radio waves generated by magnetrons—the special valves which contributed so much to the pre-eminence of British radar during the war—to accelerate the electron stream until it acquires a velocity equivalent to that produced by a potential of 4,000,000 volts. It will be so mounted that the beam may be directed into the patient at any required angle, and it will have such a high output that the treatment of large numbers of patients will be practicable. Engineers, hospital physicists, and radiotherapists have successfully co-operated in designing this high-voltage apparatus expressly for clinical work. Much of the credit for the way in which advantage has been taken of the work done at Malvern must be given to the staff of the Medical Research Council's Radiotherapy Research Unit at Hammersmith Hospital. While these five linear accelerators are being built and installed a 10,000,000-volt linear accelerator has been constructed for research purposes. It was recently demonstrated to delegates attending the Sixth International Congress of Radiology, and will shortly be installed at Hammersmith Hospital.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

CHEMOTHERAPY*—II. INDICATIONS FOR THE USE OF PENICILLIN

BY

LAWRENCE P. GARROD, M.D., F.R.C.P.

Bacteriologist, St. Bartholomew's Hospital; Professor of Bacteriology, University of London

The indication for using penicillin is not a disease, such as pneumonia or meningitis, but infection, wherever situated, by a sensitive micro-organism. This is now almost a truism, and since the advent of this and other forms of chemotherapy the profession as a whole has learned to think bacteriologically as it never did before. The laboratories are kept busy in providing the information on which rational treatment can be based. For this, it may be mentioned, they prefer a specimen obtained before treatment is begun; a short period of chemotherapy, even if not fully successful, can hopelessly obscure the picture. Naturally there are conditions, such as gonorrhoea and carbuncle, in which the bacteriological as well as the clinical diagnosis is self-evident, but even in some of these—and carbuncle is an example—it may be as well to confirm that the organism is normally penicillin-sensitive: staphylococci sometimes are not.

Sensitivity of Different Bacterial Species

In the past bacteria have been classed as either sensitive or resistant to penicillin. In fact, there is no such thing as complete resistance, but only a wide range of variation in sensitivity, the total compass of which is about 100,000-fold, and in the top ranges of this the bacteria and other organisms concerned are for practical purposes resistant, since the concentrations necessary to inhibit their growth cannot be attained anywhere in the body. At the other extreme are highly sensitive organisms, affected by concentrations easily attained throughout the body by giving moderate doses. Between these extremes there is a ladder of diminishing susceptibility with a species on almost every rung of it, and whether treatment will be of any value depends on how high a concentration can be attained at the site of infection. To maintain high concentrations throughout the body is difficult, arduous for the patient, and expensive; but to maintain them locally may be very much easier. In the central nervous system, and notably in the urinary tract, organisms which are outside the range of susceptibility for systemic effect may be successfully attacked.

If we retain the terms "sensitive" and "resistant" and make two categories of each according to their degree, some of the principal species can be classified as follows:

Fully sensitive (inhibited by 0.005–0.05 unit per ml.).—*Gonococcus; Meningococcus; Str. pyogenes; Str. viridans*†; *Pneumococcus*†; *Staph. aureus*†; *B. anthracis; Actinomyces israeli*†; *Treponema pallidum;* Vincent's organisms; *Erysipelothrix rhusiopathiae.*

Less sensitive (inhibited by 0.1–0.5 unit per ml.).—*Clostridia; C. diphtheriae; L. icterohaemorrhagiae.*

Moderately resistant (inhibited by 1–10 units per ml.).—*H. influenzae; Str. faecalis; Proteus vulgaris; Salm. typhi.*

Highly resistant (inhibited only by >50 units per ml.).—*Myco. tuberculosis; Shig. dysenteriae; Ps. pyocyanea; Bact. friedländeri;* most other Gram-negative bacilli; yeast-like and some other fungi; most viruses.

This list is far from complete, but the first category embraces the vast majority of infections for which penicillin is ordinarily used. It is noteworthy that four species in it have to be classed as variable, and in dealing with them it may be necessary to have a laboratory estimation made of the degree of sensitivity of the patient's own strain.

It is impossible within the compass of a short article to give an account, however brief, of all the possible uses of penicillin in different conditions. Many of these, however, if classified according to their causes, fall into only a few categories, in which the principles of treatment, if not its detail, are the same.

Haemolytic Streptococcal Infections

Streptococcus pyogenes of Lancefield's Group A is remarkably constant in its high degree of sensitivity to penicillin, which cannot be altered to any material degree by habituation either in the body or in the test-tube. Penicillin is therefore a dependable remedy for all infections caused by this organism, and the only serious question affecting its use concerns the merits of the sulphonamides as an alternative. Most strains are also fully sulphonamide-sensitive, and until the advent of penicillin we were perfectly satisfied with these drugs; indeed, they had brought about the greatest therapeutic revolution of modern times, and completely transformed the outlook in conditions which formerly had a high mortality. They are also cheap, easily administered, and reasonably free from risk, except in sensitized patients or those given very large doses.

Wound sepsis, acute throat infections, and puerperal fever, the three principal classes of infection which may be caused by haemolytic streptococci, can or could still be treated with sulphonamides with almost uniform success, although the response may initially be not quite so rapid as that to penicillin. Whether they should be is a matter of opinion, and involves considerations extraneous to the merits of the treatment, such as those of convenience and economy. It is perhaps reasonable to suggest that early and uncomplicated cases, at least of the first two of these classes, especially if undergoing treatment in their own homes, might be treated with sulphonamides only. Penicillin is always there in reserve should it prove to be needed. On the other hand, penicillin should be given from the first in severe wound infections, middle-ear disease, and puerperal fever, since here the inherent dangers are more immediate and less predictable, and a more rapidly acting and slightly more certain remedy is evidently called for.

Owing to its bactericidal action (that of the sulphonamides being merely bacteriostatic) penicillin is more capable of actually eliminating the organism as well as curing the disease. This is one reason for using it in scarlet fever, since it greatly shortens the period of infectivity: to ensure this effect treatment must be continued for seven days. It should not be forgotten that haemolytic streptococcal infection commonly complicates several other specific fevers, including severe diphtheria (for which large doses of penicillin are beneficial in any case) and smallpox.

*Part I appeared in the *Journal* of August 19, p. 453.
†Some strains may be less, or much less, sensitive.

Pneumococcal Infections

Pneumococci are usually fully sensitive to penicillin, but this species can acquire a moderate degree of resistance to the drug, and such strains are sometimes encountered. The same is true of their reaction to the sulphonamides. In general they are fully sensitive to the newer members of this series, but difficulties with resistant strains began to be encountered in the latter part of what may be called the sulphonamide era (1935–45); how often they occur now is unknown. There is this difference, that whereas the dose of penicillin can be multiplied twentyfold if necessary to meet this difficulty, that of a sulphonamide cannot.

The choice between the old and new treatments for the principal disease concerned here, pneumonia, must again remain a matter of opinion. It may perhaps be made on similar lines; that is to say, a mild case with otherwise favourable features may justifiably be given a sulphonamide only, whereas the patient whose condition justifies any serious anxiety should be given penicillin or both. Whenever possible the sputum should be examined, since in bronchopneumonia (and even in rare cases of lobar pneumonia) the infection may not be pneumococcal, and one of the newer antibiotics may be the only useful specific—e.g., streptomycin for *H. influenzae* or *Bact. friedländeri*. There is only one drug effective in all forms of pneumonia, virus as well as bacterial, and unfortunately we cannot afford in this country to give it to every case: this is "aureomycin."

Staphylococcal Infections

The position here is different in two ways: sulphonamides are relatively ineffective, and yet by a strange misfortune this is the one common sensitive species which sometimes possesses a high degree of resistance to penicillin. Staphylococci can in fact be rendered enormously resistant in the test-tube, but this change has nothing to do with the natural resistance which is now presenting a serious therapeutic problem: this has a different mechanism, and there is almost no doubt that selection and not habituation is the cause of its increasing prevalence. The general use of penicillin is steadily eliminating staphylococci sensitive to its action, while those naturally resistant to it survive and spread. At present the proportion of all staphylococcal infections which are due to these resistant strains appears to be only about 5% in the general population, but it often exceeds 50% in institutions such as hospitals and maternity homes: here cross-infection and the nasal carrier-state in nurses enable a resistant strain to become endemic.

There is ample proof that the degree of this natural resistance varies widely in different strains, and unfortunately its degree cannot easily be estimated. There is no general agreement on whether it can be overcome by greatly increased dosage; the truth almost certainly is that it sometimes can and sometimes cannot, depending on the degree of resistance. When it cannot, the best alternative is again aureomycin.

But for this qualification, which recent developments have made necessary, it could well be said that penicillin is more of a godsend for staphylococcal infections than for any other. It is invaluable in osteomyelitis, although here, as in any other lesion causing necrosis or suppuration, it does not remove the need for surgery. It is required for carbuncle, and may be used also in severe furunculosis and in staphylococcal infections of wounds, of the air passages, and of the urinary tract. Either applied locally or, if necessary, given parenterally, it is useful for all skin conditions of which staphylococci are the cause (sycosis, pemphigus, impetigo, blepharitis), and to some extent for any in which these organisms are important secondary invaders.

It is now advisable to consider infection in a few special situations, for which the method of treatment may be different.

The Circulatory System

Endocarditis.—It need scarcely be said that septicaemia of whatever origin, due to any sensitive organism, is the strongest possible indication for penicillin treatment. Equally so is endocarditis, whether acute or in the subacute form also known as endocarditis lenta. The treatment of endocarditis, particularly of the latter type, calls for more vigorous and sustained efforts with penicillin than any other disease. The latest conclusion reached from its study in this country is that a daily dose of two million units is advisable, and that treatment should be continued for at least six weeks. This dose should be so subdivided as to maintain a continuous effect. Among factors affecting the prognosis are the stage of the disease at which treatment is begun. Early recognition is thus vital, with repeated blood cultures for confirmation. Another is the degree of sensitivity of the organism. This is variable in *Str. viridans* and uniformly low in *Str. faecalis* and *Haemophilus parainfluenzae*, which are less common causes of the infection. Some cases will therefore require either very large doses of penicillin, perhaps reinforced with caronamide, or another antibiotic or combination of two, such as penicillin with streptomycin.

The Central Nervous System

Meningitis.—The only form of purulent meningitis which it is still advisable to treat with sulphonamides alone is meningococcal. When streptococci, pneumococci, or staphylococci are concerned penicillin must be used, and because comparatively little reaches the cerebrospinal fluid from the blood, intrathecal injection is necessary. The concentrations which can so be maintained in the cerebrospinal fluid are such that even less sensitive organisms can be attacked in this situation. These include *H. influenzae*, although streptomycin is to be preferred for this infection. Penicillin should be given intramuscularly as well as intrathecally, and when the organism concerned is also sulphonamide-sensitive one of the more potent sulphonamides which attains a good concentration in the cerebrospinal fluid—sulphadiazine being probably the best—should be given in addition.

Urinary-tract Infections

When penicillin is administered by injection some is destroyed in the body, but almost the whole of the remainder, amounting to 60% or more, is excreted in the urine. Thus if a patient is given 250,000 units a day and his urinary output is 1,500 ml., its penicillin content will be 100 units per ml., a far higher concentration than that attained in the blood or tissues. This means that infections of the urinary tract caused even by bacteria in what has been termed earlier the "moderately resistant" class may be successfully treated. The principal species, with the concentrations usually required to inhibit their growth, are:

Staphylococcus aureus and *albus* ...	0.02	unit per ml.
Streptococcus faecalis	2	units per ml.
Proteus vulgaris	8	units per ml.

Even some strains of *Bact. coli* are sensitive to about 25 units, although others are more resistant. *Bact. aerogenes*, *Ps. pyocyanea*, and various paracolon bacilli are

highly resistant, and penicillin is useless for them. Penicillin can thus be used for some urinary-tract infections, but only with any expectation of success if the nature of the infection is known and comes within no more unfavourable category than the "moderately resistant." Large doses are not necessary, but they should be given at least four times a day unless in a slowly absorbed form. No attempt need be made to alter the reaction of the urine, but output may with advantage be diminished by restricting fluid intake.

Prophylactic Use

The use of penicillin to prevent infection in very varied circumstances has become common, and a few personal opinions on some of these types of use may perhaps be expressed.

At least three seem fully justified. One is the prevention of infection in extensive and grossly contaminated recent wounds. The effect of the intramuscular penicillin given to casualties with the more dangerous types of wound during the attack on Normandy in 1944 astonished and delighted everyone who saw these men, and there is no doubt that this example should be copied in dealing with all wounds involving serious danger from sepsis generally and gas gangrene in particular. Another imperative indication is dental extraction or tonsillectomy in a rheumatic subject, or indeed in anyone in whom the temporary bacteriaemia now known to be produced by these operations is likely to have any consequences. A third is prolonged labour with much manual interference, or any other circumstances particularly tending to infection of the placental site.

It is more doubtful whether penicillin should be used as a preventive of infection during the course of what should be a clean operation, or of post-operative chest complications. This sort of use is often unnecessary, wasteful, and not always successful, since infections, particularly of the chest, do occur in spite of it, and are then usually due to penicillin-resistant bacteria. It can be said even more emphatically that penicillin given alone is not a reliable preventive of infection in connexion with operations on the urinary tract. The majority of the Gram-negative bacilli apt to cause this are not merely resistant to penicillin : they appear to thrive on it. This is not simply a figure of speech : there are good reasons for believing that *Ps. pyocyanea,* for instance, is actually stimulated by penicillin, and it is not very uncommon for a urinary-tract infection to be produced by this organism *de novo* in a patient having a long course of penicillin treatment, for no other apparent reason than that the drug is being given. If penicillin is considered necessary to prevent tissue sepsis due to cocci, then a sulphonamide should be added to give wider cover for the urinary tract itself.

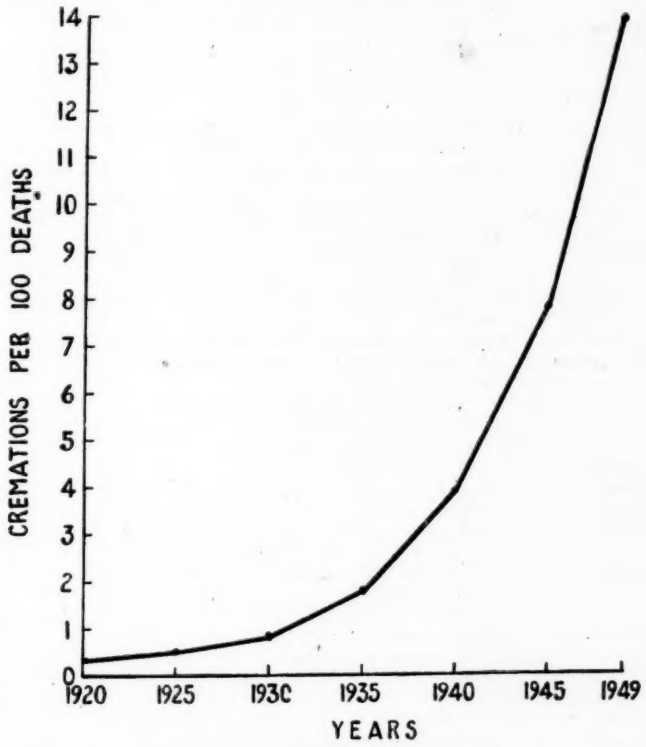
Reference to the list of the principal sensitive bacteria will serve as a reminder that penicillin can be used in a number of other diseases, for which there is no space for further discussion. On the other hand, it is without action in many other infections, and some of these are susceptible to the newer antibiotics, which are the subject of two articles to follow.

Impact, a quarterly bulletin issued by Unesco, gives reports of addresses and notes on books mainly on the theme of the impact of science on society. The first issue, which is dated April–June, 1950, includes a short introduction on the main theme, to which is attached a bibliography with notes on the books listed. The bulletin is obtainable for 3s. a year from the Unesco Sales Service, Unesco House, 19, Avenue Kléber, Paris, 16e.

CREMATION

COMMITTEE AND CRANK

Disposal of the dead by cremation has become increasingly popular in the last thirty years. According to a recent report of the Cremation Committee[1] there were 1,796 cremations in 1920 and 79,607 in 1949. The following graph shows the number of cremations per 100 deaths in England, Wales, and Scotland in certain years from 1920 to 1949.



The committee was appointed in 1947 to review the regulations made under the Cremation Act of 1902, and to make recommendations. Its members were: Mr. H. A. Strutt (chairman) and Mr. R. S. Wells, of the Home Office, Mr. R. Howat, of the Department of Health for Scotland, Mr. J. M. Ross, of the General Register Office, and Mr. H. F. Summers, of the Ministry of Health.

Medical Certification

The regulations were framed primarily to prevent cremation being used to destroy evidence of crime. The normal medical attendant of the deceased gives a detailed certificate leading up to the opinion that there is no reason to suspect that death was due to other than natural causes (Form B); and an independent medical practitioner gives a shorter confirmatory certificate (Form C). Alternatively, a medical certificate (Form D) may be given by a pathologist who has conducted a necropsy on the case, or by the coroner (Form E). Authority to cremate is given by the medical referee (Form F).

The committee's main recommendations on medical certification are as follows:

The certificate in Form B should require further and more explicit details: (*a*) Where the medical attendant has consulted the coroner, the fact and the result should be stated on the form. (*b*) It should be stated whether or not a post-mortem examination has been made, and, if so, by whom it was made, and the result. (*c*) Particulars should be given of the date of any operation during the final illness or within a year before death. (*d*) The present question No. 13 should make it clear that the reference here is to private nursing. (*e*) The medical attendant giving the certificate should furnish his

[1] Report of the Interdepartmental Committee Appointed by the Secretary of State for the Home Department, 1950. (H.M.S.O., 9d.)
[2] *British Medical Journal*, 1880, **2**, 461.
[3] Ibid., p. 794.
[4] Ibid., 1884, **1**, 123.
[5] Ibid., p. 515.
[6] Ibid., p. 624.

address and telephone number. (*f*) Dual questions should be set forth as separate questions.

The requirement that Form B must be completed by a medical attendant who attended the deceased during his last illness should be varied to permit certification by the doctor "to the best of his knowledge and belief" if he had visited the deceased within 14 days prior to death.

The requirement that the medical practitioner completing Form B must certify definitely the cause of death before cremation may take place should be modified to permit the confirming doctor to authorize cremation where there is no reason to think that death resulted from other than natural causes.

The confirmatory certificate should be retained and serve the dual purpose of confirming the certificate B and authorizing cremation, combining the present functions of Forms C and F.

This combined certificate should be given by the medical officer of health of the county or county borough in which the death occurred, the M.O.H. of a county to have power to delegate in appropriate cases to M.O.H.s of county districts. The medical officer of health should be assisted by a panel of medical practitioners chosen by the local authority.

In the case of a death in a hospital which is not referable to the coroner, the medical superintendent or his deputy should give the combined confirmatory certificate and authority to cremate.

In any case in which there may be conflict of medical opinion as to the cause of death, but in which there is no reason to suppose that the death may have been due to poison, to violence, to any illegal operation or to privation or neglect, the confirming doctor should be empowered to authorize the cremation without requiring any further examination of the body.

Any suspicious case should be reported to the coroner by the doctor giving the confirmatory certificate. If the coroner is satisfied that an inquest or post-mortem examination of the body is unnecessary, he should have power to authorize the cremation to take place. He would do this on Form E. The coroner should be empowered to authorize cremation on Form E in any case of accidental death, without waiting for the termination of the inquest.

In every case in which a coroner issues a certificate on Form E, that document should be the authority to cremate. Where the coroner, after being consulted by the doctor who gives the confirmatory certificate in Form C, does not think it necessary to hold an inquest or to make a post-mortem examination, the doctor who gives the certificate should authorize the cremation to take place. A note should be made on Form C by that doctor that the coroner has been consulted.

The Confirmatory Certificate

Some witnesses before the committee recommended abolition of the confirmatory certificate. Among the reasons for this suggestion were that the certificate was given in a perfunctory manner because the certifying doctor would not be disposed to act inquisitorially in respect of the medical man who gave Form B, and some fatal poisons might escape detection from a superficial examination of the body.

The B.M.A. in its evidence strongly opposed abolition of the confirmatory certificate, which it considered was a public duty that the medical profession should be required to take seriously. The Association emphasized that to place the onus on a medical referee alone would be to burden him with undue responsibility, and would lead inevitably to unnecessary distress to the relatives when he exercised his discretion to direct pathological examinations. The requirement that two medical certificates should be completed by medical practitioners unrelated to one another, either professionally or in law, was considered to be sound and in the public interest.

The committee also makes a number of recommendations to regulate the procedure at crematoria and to ensure that the staff should be suitable.

Sanitary Advantages

An early advocate of cremation in this country was Sir Henry Thompson, a well-known surgeon, who was one of the joint founders of the Cremation Society in 1874, among the other founders being Mr. (later Sir) Spencer Wells and Dr. Ernest Hart, editor of this *Journal*. At the B.M.A. Annual Meeting in 1880 Spencer Wells[2] read a paper on cremation in the Section of Public Health, his theme being that "the sanitary advantages over burial in coffins or in wicker baskets are undeniable and very great." He referred to Darwin's observation that earthworms bring soil to the surface from a considerable depth. He then pointed out that Pasteur had shown how the earth mould brought up by worms in fields where cattle had been buried after dying of "charbon," or splenic fever, contained "the specific germs which propagate the disease." The same germs had been found in the intestines of the worms.

As a result of this paper over 120 members of the B.M.A. sent a memorial[3] to the Home Secretary saying that "we disapprove of the present custom of burying the dead and . . . until some better mode is devised we desire to promote that usually known as cremation."

Four years later public interest was excited by the actions of a surgeon, Mr. William Price, living in Glamorganshire, an eccentric character who claimed that he was a descendant of the ancient Druids.[4] One night "attention was directed to a large fire in the grounds adjoining his house; and he was found to be in the act of cremating, in a barrel containing paraffin oil, the body of the illegitimate child of his housekeeper. He was chanting the supposed Druidical incantations over the body; and threatened to shoot anyone who interfered with him." But he was seized by a constable and conveyed to the police station. The housekeeper was later locked up because she refused to give evidence as to maternity at the inquest. Mr. Price admitted that he was the father of the child, and said that it had died of convulsions. The mother afterwards corroborated Mr. Price's evidence, and was released from custody, a verdict of death from natural causes being returned at the inquest. The body was returned to Mr. Price, who undertook that it would be interred in the ordinary way.

Mr. Price was then charged with misdemeanour, but was acquitted at the Glamorganshire Assizes by Mr. Justice Stephen and a jury, a decision which this *Journal*[5] "hailed with great satisfaction," remarking "that clean ashes are surely less repulsive to contemplate than mouldering carcasses." Mr. Price, unrepentant after all, soon accomplished his object. The body was cremated[6] on a pile consisting of three hurdles, half a ton of coal, and pair of large iron grates, Mr. Price chanting "an ancient sacred song in the presence of a number of spectators."

A Bill to regularize cremation was introduced into Parliament the same year, 1884, but was rejected, and it was not until 1902 that an Act was passed prescribing the conditions under which cremation should take place.

WORLD FEDERATION FOR MENTAL HEALTH

[FROM A CORRESPONDENT IN PARIS]

Psychiatrists, psychologists, sociologists, and psychiatric social workers from 25 countries assembled in Paris from August 31 to September 7 for the third annual meeting of the World Federation for Mental Health. The World Federation "stemmed"—to use a word which is at present in favour in this field—from the memorable London Congress on Mental Health two years ago, and its establishment and survival in face of obvious difficulties, especially financial ones, are due above all else to the driving force of its director, Dr. J. R. Rees.

The Paris meeting, which was held under the presidency of Professor WILLIAM LINE, of Toronto, was on four topics—namely, mental health in education, from the pre-school child to the education of teachers and medical men; occupational and industrial mental health; mental health of transplanted and homeless persons; and leadership and authority in local communities.

Collaboration with W.H.O.

An official welcome was given to the Federation by representatives of the French Ministries of National Education, Labour, and Public Health, and by Professor P. Heuyer and Dr. Xavier Abeley on behalf of French psychologists. Dr. G. R. HARGREAVES, chief of the Mental Health Section of W.H.O., spoke on collaboration between the Federation and his organization, pointing out that governmental and non-governmental agencies were complementary, not overlapping. He answered those who objected that W.H.O., like other instruments of the United Nations, moved slowly. He asked whether it moved more slowly than their own Governments. The time had come to shift the inquiry into the efficiency and speed of the

machinery from the international centres at Geneva or elsewhere to the national components. He quoted his chief, Dr. Brock Chisholm, as stating that perhaps the success of W.H.O. should be judged not by the amount of money which it could persuade its member Governments to spend in the international field, but by the amount which it could persuade them to spend on health in their own countries.

In his presidential address to the World Federation, Professor LINE made the point that the man in the street had confidence in the leadership of medicine so far as his physical needs were concerned, and was content that medicine should advise public-health departments in the interests of his own physical and environmental well-being. He had in fact handed over his responsibility in this respect to professional medicine, and medicine was worthy of the trust. But the man in the street must be made to realize that in the field of mental health, involving the effectiveness with which he could live with other people and with himself, he could not afford to delegate his responsibility. This was something that could not be turned over to the expert because it concerned personality development, character formation, and social adaptation, which last was expressed in that loosely used word "democracy."

The Language of Science and of Industry

The discussion on mental health in industry was opened by Dr. R. F. TREDGOLD, who made the point that it was not so much more knowledge on this subject which was required, as the better application of the knowledge already existing. He also said that the results of scientific research were quite frequently made public in a manner as remote as possible from the understanding of the industrialist, who was expected to approve them and incorporate them in his organization. The language of science was as far apart from that of industry as English was from French—indeed, it was farther apart, because when the industrialist came upon scientific language (which he was apt to call "jargon") his inhibitions were at once aroused, and he tried not to understand it, whereas the Englishman, faced with a presentation in French, regarded it as a challenge and did his best to understand it. The psychiatrist, said Dr. Tredgold, should be aware of the suspicion and uncertainty with which the industrialist regarded him. A frank statement of his aims, qualifications, and practices was at least the first step towards a better understanding.

He reminded the assembly of three cross-currents which were now operating: (1) while all were agreed that prevention was better than cure, preventive work was less attractive to the student and to the practitioner; (2) the advance of psychiatric treatment during the last 20 years, and perhaps the next 10, might gradually result in a diminution of the "chronic" population of mental hospitals, and thus release many psychiatrists for fields of work outside the hospitals; (3) in spite of what he had already said about the latent antagonism of the industrialist, it already seemed to be accepted by industrialists, who had the reputation of being hard-headed business people, that in financial terms the value of such mental-health services as had been planned and put into operation in industry had been worthy of their support.

Displaced Persons

The subject of the mental health of homeless and "transplanted" persons was developed by Professor JOHN COHEN, professor of psychology in the Hebrew University, Jerusalem. Human transplantation, he said, was as old as Adam. In fact, Adam was the first transplanted person, and perhaps his transplantation to a less comfortable environment might account for the delinquency of one of his offspring, who slew his brother. Moreover, displaced persons were not only groups vaguely thought of as moving about rather aimlessly in distant parts of the world, but were in our own community—the child taken from home to hospital, the old person removed from domestic independence to a home for the aged, the conscript entering the Army. What was new in the situation, he said, was not the phenomenon itself but the deliberate attempt or intention to reduce its hardship and to dovetail the life of the newcomer into that of the receiving community. The integration was always going on, and there were indices by which its process could be measured—the comparative literacy of the immigrants and the native groups, the extent of inter-marriage, the vital and morbid statistics of each, and the comparative industrial productivity.

One aspect of the problem of integration was the elimination of tensions. Tension, said Professor Cohen, was a central concept in psychology. It was a pity that it had been rather isolated from other concepts such as frustration and conflict, for all three cohered in the same framework. Each type of frustration or conflict produced a different kind of tension, and an analysis of these different forms of tension, above all in the social sphere, should be attempted.

One of the reports presented to the meeting concerned the results of an inquiry into training facilities in psychiatry and allied mental-health disciplines. Replies so far have been received from no more than a dozen countries, not including Great Britain. The replying country in which there is the most abundant provision is the United States. At the present time the approximate annual output of trained psychiatrists from training institutions in the U.S.A. is 500. It is estimated that approximately that number of medical graduates complete each year a comprehensive systematic training course in psychiatry covering a period of three years. There are 253 hospitals, institutions, and other training centres in the U.S.A. which are recognized by the medical profession as providing acceptable training. Three-year advanced training courses are provided by 10 approved psycho-analytic institutes, and an average of 21 psycho-analysts complete this training annually.

Nova et Vetera

GIORDANO BRUNO AND THE CIRCULAR MOTION OF THE BLOOD

So far, Giordano Bruno (1548–1600), the philosopher of pantheism and martyr of science, does not seem to have been cited in connexion with the discovery of blood circulation. I have no intention of claiming a share in this discovery for Bruno. I wish, however, to put on record several passages in which Bruno emphasizes the "circular" pattern of the motion of the blood. He says: "The spiritual life-force is effused from the heart into the whole of the body and (flows back) from the latter to the heart, as it were from the centre to the periphery and from the periphery to the centre, following the pattern of a circle. . . . The material part of all these spirits is a fluid which cannot move on its own account, but by means of its innate spirit. Hence there is no circular or sphaerical motion outside the body, for the *blood, which in the animal moves in a circle* in order to distribute its motor, the spirit, lies immovable outside the body, is inert and decays, no longer deserving the name of blood" (*De Rerum Principiis.* 1590. A certainly genuine though posthumous treatise from the "Noroff Collection," edited by F. Tocco and H. Vitelli. Opp. Latina. Florence, 1891, p. 521.).

He also says that "in us the blood and other fluids are being *moved continually and very rapidly in a circle*, flow and flow back, are diffused from the centre into the extreme periphery and from there return to the centre—a movement for which the followers of Aristotle give far-fetched and confused reasons such as an instinct of nature, the necessity of fate, the providence of God, etc." (The italics are mine.)

There are also allusions to the circular motion of the blood in two of his better-known treatises (*De Immenso*, VI, 8; *De Monade*, 1591, p. 23). The ideological background to this is (*a*) his most probable acquaintance with Caesalpino, the well-known Aristotelian philosopher, naturalist, and precursor of Harvey, the first to use the term "circulatio" (1571), and (*b*) Bruno's belief in the perfection of the circle as the fundamental symbol of all life and action in the cosmos (*De Triplici Minimo*, I, 3; *De Monade*, I, 2). The above passages from Bruno show that Caesalpino's idea of "circulatio" was alive in a general philosophical form towards the end of the sixteenth century.

WALTER PAGEL.

Correspondence

The Difficulty in Medical Education

SIR,—Your educational number was highly entertaining, but the contributors do not appear to have grasped the real difficulty in medical education, which is that people cannot avoid preaching what they practise. The preclinical teacher practises medicine as a branch of inductive science, the hospital consultant practises it as a specialty, and the whole-time clinical professor, restricted to a small unit, practises it as a means to clinical research. None of these practices has much relevance to general practice. The ideal medical school would be different from either a university or a key hospital; I often think it would come better outside and after the university. So long as we go on expecting to prepare students for general practice in institutions which have a different frame of reference we shall continue to be dissatisfied with the results.—I am, etc.,

Oxford. L. J. WITTS.

Training for General Practice

SIR,—In his article, "A G.P. on his Clinical Training," Dr. Donald Johnson writes (*Journal*, August 26, p. 493) of his hospital education in preparation for general practice as having been "wholly bad." He is writing of 25 years ago when he spent two years and six months as a medical student at St. Bartholomew's Hospital. As I am no longer a member of the teaching staff of that hospital, I may perhaps be allowed, without prejudice, to explain to Dr. Johnson how it is that he has become a competent general practitioner in spite of (because of) Bart's. The same post which brought me the *Journal* with his article in it brought me a brochure about the Paget Club, which is one of our institutions at St. Bartholomew's. This brochure opened with the words: "Sir James Paget, 'Nothing appears more certain than that the personal character, the very nature, the will, of each student had far greater force in determining his career than any helps or hindrances whatever'—('What Becomes of Medical Students,' *St. Bartholomew's Hospital Reports*, 1869, 5, 242.)"

St. Bartholomew's Hospital, with its tradition, atmosphere, teachers, nurses, porters, and students, strengthened Mr. Johnson's character and will. *We made the man* and he became a good doctor, partly because we made him, or we left him, hungry for knowledge. He tells us how, after leaving the hospital, he gained valuable clinical experience in the Metropolitan Hospital, Kingsland Road, how he learnt about the treatment of minor complaints from the experienced G.P. from whom he bought his practice, and about skin diseases from his dispenser. His article is that of a man with strong convictions; it is boldly critical, and he tells us that he is a pretty good doctor ("reasonably competent," he says). He is in fact a good Bart's product, and it is doubtful if he would have turned out any better if he had done his clinical training in a tip-top spoon-feeding unit.—I am, etc.,

London, W.1. GEOFFREY EVANS.

SIR,—Despite the publication of enlightened protests, such as that of Dr. Donald Johnson (August 26, p. 493), against the process of standing six months in a theatre catching glimpses of specialized surgical operations or of parking one's posterior on the patient's bed-locker during interminable ward rounds, students still come to be qualified without an adequate idea of how to work in general practice.

It is refreshing to read in an article by Professor W. Hobson and Dr. J. Pemberton in the *Lancet* this week (August 26, p. 324) that at Sheffield:

> "In the final three months of his curriculum each student will be attached to a general practitioner for a fortnight. He will attend the morning surgery and accompany the general practitioner on his daily round. In this way he will see for himself the opportunities open to the doctor for practising social medicine in the community."

These fortunate students should be able to see many other sides of medicine, and particularly those which are neglected in their hospital experience. May I repeat what I said at the meeting of members of the Royal College of Physicians at which Dr. Lawrence spoke? If I had a child who was taking up medicine I should make sure that he or she had at least three months' "apprenticeship" to a good general practitioner. Thinking it over, I am inclined to suggest six months; one period of three months before going to walk the wards and another after that, but before taking finals. Could not this sort of apprenticeship be made compulsory and interchangeable with six months of the new compulsory intern year?

Finally I still have a dream, which is unlikely to come true, of a general practitioner being allowed to attend all lectures and ward rounds where students are instructed, and his being given five minutes at the end to tell them how much they may forget. (Perhaps five minutes would not suffice.) This is obviously impracticable, but might not each teacher carry in his mind a similar imaginary counsellor to stop him from wasting the students' time?—I am, etc.,

Bristol. HUGH R. E. WALLIS.

SIR,—Heavier bludgeons than mine will, I feel sure, be swung at Dr. D. McI. Johnson (*Journal*, August 26, p. 493). I feel compelled, however, to make a pass at him myself. He has put himself, it is true, in a strong strategic position; anyone who blames himself and not his teachers for what he failed to learn 25 or more years ago can easily be disposed of as self-righteous. May I suggest that Dr. Johnson explains nearly the whole of his let-down by Bart's in the words "somewhat unwilling but not entirely uninterested"?—I am, etc.,

Potters Bar. W. E. HAYES.

SIR,—I have read with much interest Dr. Donald Johnson's article in the *Journal* (August 26, p. 493).

I had no idea that, 25 years ago, the clinical teaching at St. Bartholomew's was so primitive. At Edinburgh—but that was 50 years ago—we had the most excellent clinical teaching, which covered the needs of the embryo G.P. or specialist. Ward rounds (I do not remember tired legs); side-room talks; out-patients; evening tutorials; anaesthetic giving, with the not uncommon sequel of instruction in artificial respiration—all gave us the chance of assimilating what was to be of future use: "You mustn't mind seeing these cases frequently. You'll see lots in G.P." (Cotterill). "Handle the patient's body as if it were your own" (Chienne). "This is the sort of puzzle you'll meet in practice" (Bramwell). And so on.

The defects in my methods, which may be so obvious to my colleagues, I can fairly put down, with the modesty so characteristic of the southern Scot, to my own lack of attention, or of the ability to absorb. The material was presented well; it was up to me to digest it. Two or three years later I adopted what I think should be a universal practice (even for medical scientists—it will broaden their minds). I went as assistant to a first-class G.P. In a small country town on the Scottish borders Dr. David Huskie gave me the chance—may I have taken at least some of it—of learning how to approach patients, how to bear adversity, how to give the gentle answer, to see and how to treat the minor and chronic ailments which are inevitably not seen in hospital, how to shoulder responsibility.

I agree wholeheartedly with Dr. Johnson in his condemnation of systematic lectures, a complete waste of time in that we wrote instead of listening, and I thank him for spurring me on to pay a belated tribute to my old hospital and my old chief.—I am, etc.,

Glamorgan. A. W. B. LOUDON.

SIR,—Dr. D. McI. Johnson's diatribe against the clinical teaching he received at Bart's (*Journal*, August 26, p. 493) should, of course, have the heading "Stinking Fish."

As one who must have been a contemporary of Dr. Johnson may I say: (1) I thought then, and still do, 22 years afterwards, that I was made to learn many things that have been no use to me since. (2) This does not alter the fact that the picture he draws of the futility of Bart's teaching then is grossly exaggerated. (3) There must be many old Bart's men who are

eternally grateful for the teaching of men like Horder, Gow, Vick, Rawlings, Patterson Ross, Kenneth Walker, Roxborough, Girling Ball, Wilfred Shaw, Langford Moore, and a host of other grand teachers too numerous to mention. (4) Dr. Johnson blames his teaching for not foreseeing early death after a hemiplegia. Why? The best bedside clinician cannot always foretell the outcome of these cases. (5) He complains that he could only write two prescriptions. Why? Had he never read and resorted to the Bart's Pharmacopoeia, or was this included in what he, in his wisdom, "ruthlessly eliminated" from his programme? (6) He could not give "even a hypodermic injection." Why? I seem to remember we all had ample opportunity to learn this simple job. (7) He knew nothing about rashes, infectious or non-infectious. Did he never attend Skins or Fevers? What was he doing all the time? And the final absurdity—of which we have heard *ad nauseam* from other sources—"Society, shocked at the incompetence and inexperience of newly qualified doctors . . ." Let us have evidence of the proof of this statement. What "Society," or branch or faction of it? What "incompetence" has been a nine days' wonder?

I am old-fashioned enough, Sir, to believe in loyalty. Loyalty to one's team, one's crowd, one's Alma Mater. And I for one will always be glad and proud and happy that I went to Bart's and that I have tried to live up to, and profit by, all that Bart's has taught me.—I am, etc.,

Aylesbury. W. A. BELLAMY.

SIR,—I take a hasty pen to protest how very different from the curriculum described by Dr. D. McI. Johnson (August 26, p. 493) was the teaching at Guy's about fifteen years earlier. On reaching the clinical stage a student became a ward-clerk. A firm, maximum six, had about seventy beds between them, and certain hours, extensible to taste, in the "Front Surgery." The clerks were immediately responsible for case-history of all admitted cases, with all signs and symptoms they could detect. Later the registrar took the firm round, with criticism and coaching; and when the consultant had made one more round there would not be very much unelicited about these cases, especially as questions were searching and treatment and progress had to be meticulously noted. There was much rivalry between firms, and efficiency was checked by interim examination.

Work in Casualty or "sorting" department was under supervision by dressers and house-surgeons, and all the way up the scale there was an admirable blend of responsibility with guidance. We were not forced into P.-M. room or museum, but the wisest spent many hours there. For those aspiring to house appointments there was a ward called "Clinical," where one had one's own beds and had first choice of all cases admitted to the hospital.

As regards special departments, we were encouraged to believe that the G.P. was the backbone of the profession, and should know enough of all branches to do some good and no harm. Skin Out-patients in particular was always crowded, and thought to be about the best value per man-hour to be obtained. There was always so much of interest going on in the hospital, including "culture," that there was little temptation to seek it elsewhere; nor, considering all there was to learn in a brief four years, did the less brainy of us find much time to do so, after taking a fair share of athletics.

A graduate trained only in a general hospital must inevitably lack much knowledge of minor ailments and chronics, but how better gain the lacking experience than by six months as assistant to an "old-timer"?

Dr. Donald Johnson seems to have found standing round beds a trial; but we were all young once, and a posse (or is it a fleet?) of bath-chairs would be somewhat of a traffic problem.—I am, etc.,

Kington-on-Arrow, Herefordshire. G. W. DRYLAND.

SIR,—I have only just read Dr. J. H. S. Hopkins's article on Bornholm disease (May 27, p. 1230). It is an extremely common condition. Practitioners should try to get all their cases of this and of atypical pneumonia as fully investigated as laboratory facilities allow. It is a "pushover" as a subject for an M.D. thesis. My experience has been that physical signs are usually present, but I have made embarrassing misdiagnoses.

Early descriptions of outbreaks in nursing staff and failure to instruct students about the disease are related phenomena and the usual hallmarks of impending dissemination of knowledge of common, interesting, and overlooked diseases. All students are well instructed in the pathology, aetiology, and differential diagnosis of the rarer, progressive, serious, and fatal illnesses. These are also in the books, where you can look them up if you did not attend ward rounds. Teachers neglect the common ones because they know nothing about them. Their only contact with everyday disease is in themselves and nursing staff. (Note the reluctance with which some consultants approach the sick nurse or student.) Serious disease eliminated, analytical thought and further investigation are abandoned. For this there is some slight excuse. However, they fail to teach the management of cases. Hence modern insistence on a doctor doing a few house jobs. If he does them in a municipal or non-teaching hospital an intelligent man soon picks up a working knowledge of medicine.

I qualified without having been shown any of the common infectious fevers except chicken-pox. Fortunately I had had the others, but this experience is not universal. However, if I saw a case of aortic stenosis I knew the patient was usually a man; and that a child with chorea is usually a girl (this is more useful).

Any general practitioner of sound intelligence who analyses his cases carefully will cut clean through the mass of inexperienced consultants to the top, as witness Mackenzie—provided he advertises by writing. If he does not do this he is merely a miser deriving pleasure from his hoard of superior knowledge.—I am, etc.,

Co. Derry. D. HAMILTON, Capt., R.A.M.C.

Psychology as Science

SIR,—Dr. F. M. R. Walshe, in his Linacre Lecture (*Journal*, August 12, p. 379), has paid me the compliment of referring to a work which I wrote a quarter of a century ago. In the naturally brief summary which he sets out I do not feel that he has given a correct picture of the position which I adopted in that book, and I am therefore seeking this opportunity to make my position clearer.

He accuses me of claiming that psychological medicine has established itself as a discipline within the field of the natural sciences, that the data of the psychologist in medicine are strictly comparable in character to those of natural science, that—as a scientific concept must be capable of verification by repeated reference to experience and experiment—I clearly believe this postulate to be fulfilled in psychological medicine. There are other accusations which I will refer to later, but may I in the first place be allowed to plead not guilty to these preliminary charges, basing my defence entirely on the statements made in the book in question? To begin with, I did not claim that psychological medicine had established itself as a discipline within the field of the natural sciences. On the contrary, the whole aim of the book was to examine whether and how far psychological medicine could claim a place within the field of *Science*. Science is not here equated with "natural science," and Dr. Walshe would obviously agree with me in this respect, as he uses the term "historical science." The meaning which I attached to "science" was the employment of the method of science as defined by Karl Pearson—viz., a procedure involving three successive steps. First, the observation of phenomena; secondly, the orderly arrangement and classification of the facts which have been observed; and, thirdly, the finding of "laws" which will serve to explain those facts, and enable one to predict and control the occurrence of future phenomena of the same order. The object of my book was, as I have said, to examine to what extent the development of psychological medicine had followed this road. While I found that it had done so in certain respects and at certain stages of its growth, in other respects and particularly in some of its later stages I emphatically stated that the canons of scientific validity were not satisfied. I described my final position with regard to these

later developments as one of "benevolent scepticism." I share the substantive with Dr. Walshe, though hardly the adjective.

Next, so far from claiming that the data of the psychologist are strictly comparable to those of natural science, I have expressly set out their weakness in this respect. Except for the facts of introspection all other psychological facts are inferences, in that they are inferred from behaviour and speech. I quoted Drever's remark that this peculiarity was an inherent weakness, and one which dooms psychology always to occupy an invidious position in the scientific hierarchy. I added that, owing to the nature of its material, psychology can give only an imperfect response to the demand for objective verification which science insistently makes. Nevertheless I did not, and do not, think that this weakness is sufficient to remove psychology altogether from the employment of the method of science. Often the gap that separates the "psychological fact," which forms the material to which psychology applies the method, from the directly observed fact—e.g., speech—is so small that it may safely be neglected. After all, inferences of this degree are commonly accepted in medicine. If a patient tells me that a spot is tender, I include the tenderness without protest among observed facts, though it is actually an inference. I do claim that, by following the method of science, psychological medicine has in its development arrived at conceptions which serve to explain and control our experience to a degree which no other mode of attack has succeeded in achieving. I may cite here the work of Janet on hysteria, which cast a new light on a field illuminated before only by the completely sterile concept of "functional nervous disorder" bequeathed by our neurologist ancestors. Moreover, this work was to a reasonable extent capable of being checked by experience and experiment. I would also add the conception of "purpose" in disorder, which we certainly owe to Freud's earlier work. This conception enabled us to understand the genesis of the psychoneuroses of the first world war, and moreover the knowledge so gained enabled practical and effective steps to be taken in controlling and reducing similar manifestations in the second world war. It is perfectly true, therefore, that in my book I claimed that psychological medicine had, by employing the method of science, succeeded in making considerable advances. But, in estimating that success, the gap between the actual observed fact and the psychological fact behind it must be carefully watched, and the possibility of distortion between the two borne constantly in mind. In the later work of the Freudian school I felt that the gap had been too wide, and I therefore was not prepared to accept it as conforming to the postulates of scientific method.

I may remark here that the context of Dr. Walshe's lecture makes it plain that he is identifying psychological medicine with the doctrines of the orthodox psycho-analytic school. He pays no attention to the very considerable work which has been and is being accomplished altogether outside that school. This point does not directly concern me, however, except in so far as Dr. Walshe has by implication included me with those accepting the Freudian claims.

One further accusation of Dr. Walshe must be mentioned. Commenting on my remark that the introduction of "purpose" removes psychology from the mechanistic sciences, but not from the whole field of science, he says, "Here Hart seems almost trembling on the brink of awareness that psychology does not belong to natural sciences. However, he goes on to place it with biology. Yet the word 'purpose' is not unequivocal, for teleology in biology is not the 'purpose' that determines human action. Such are the pitfalls of linguistics." I understand this quip to mean that I have unwarrantably identified "purpose" in psychology with teleology in biology. If I had done so I should not describe my transgression as having anything to do with linguistics, but should term it a gross confusion of thought. But I perpetrated no such error. The gist of the whole passage in question is as follows. There are two concepts of causality: (1) An unconditional sequence; *a* is inevitably followed by *b*. (2) Not merely inevitable succession but a relation of identity between cause and effect. The effect is regarded as the cause in a new form. In this sense causation is an equation, and a reversible equation. It is the sense in which causality is understood in the mechanistic sciences, and obviously psychology cannot be brought under it, for sequences in which "purpose" is playing a part are clearly not reversible. But this irreversibility does not exclude psychology from the first concept of causality. If it were insisted that the method of science requires the concept of causality in the second sense, biology and even physiology would have also to be excluded, not because teleology and "purpose" are identical, but because both necessarily involve irreversible sequences. They are analogous in this attribute of irreversibility, but that is all.

In my book I pointed out that I held no brief for regarding the method of science as a unique mode of approach to the problems of psychology, and was quite prepared to employ any other method which should prove to be more effective. Dr. Walshe now puts forward the method of historical science as the only sound alternative. He does not give any concrete example of the use of this alternative in the problems of psychological medicine, and we could of course hardly ask for this in the scope of a single lecture, though I hope he will give us further indications of his proposals in this respect. But I must confess that I feel considerable apprehension over his comparison of the historical method of approach with the taking of a clinical history. In the latter, as he rightly says, "From its items we select, discard, and assemble in the light of our previous experience; and the final product of our activity is the sublimation of a certain kind of evidence from one source and of a critical study of it from another," and later he speaks of the ideal medical psychologist dealing with the mental activities he is examining "by rethinking or reliving these activities in his mind, and in the context of his own knowledge." The possible action of bias and distortion here is so great that my feeling of helpless scepticism, in face of the labyrinth of conflicting speculations and methods which Dr. Walshe so eloquently describes, is far from being assuaged. It is very doubtful whether the clinical history obtained by Dr. Walshe in a given case would be identical with that obtained by an enthusiastic psycho-analyst in the same case. I would point out that the advance in historical method which has taken place in the last century is largely due to a better estimation of the part played by bias and emotional distortion in presenting alleged factual records, and this has been achieved by the application of psychology to historical method, rather than vice versa. Some of this knowledge, indeed, has been attained by the use of investigation and experiment—e.g., by Stern and the Breslau school—which needs no apology on the score of scientific method.

Finally I would say that one of the lessons of history is that systems of thought and belief are destroyed, not by attacking them, but either by a process of internal decay or by the appearance of another and more satisfying system which gradually undermines it. I would be content to leave the developments which Dr. Walshe anathematizes to the first process, in the hope that a considerable sediment of solid stuff would be left. But if Dr. Walshe can really provide the second alternative it is cordially to be welcomed. For my own part I felt when I wrote the book, and still feel, that psychology will get along better by pushing the method of science, albeit in an imperfect form, as far as it will prove reasonably sound and effective, than by any other method as yet available.—I am, etc.,

Eastbourne. BERNARD HART.

SIR,—In his most interesting Linacre Lecture (August 12, p. 379) Dr. F. M. R. Walshe writes; "Of its possible relation to historical science we find no word in the superabundant writings on psychological medicine" (p. 382). May I be allowed to point out that in the preface to the fifth edition (1944) of my *Psychology and Psychotherapy* I wrote:

"Psychology as a science is based on the category of historical causation, and the rules of diagnosis and prognosis in medical psychology are based on patients' medical histories supplemented by the results of deep mental analysis. It is instructive to re-read Immanuel Kant's *Kritik der reinen Vernunft* from the standpoint of modern historical science. Events do indeed follow one another 'according to a rule' (*nach einer Regel*), but deeper connexions of meaning have to be unravelled before the true 'rule' becomes apparent."

As one listens to a patient during a course of prolonged and deep mental analysis, one is impressed by the importance of

"choice" and "decision" at critical moments of his life, and one sees his life unfolding as an evolutionary process and not as a mere mechanical sequence of events. My experience in the consulting-room, in association with my training as a philosopher, has convinced me that individual mental life is a historical process, and that the mental sciences (*Geisteswissenschaften*) reach their fullest development along the lines of historical explanation. But this, of course, leaves scope for many other legitimate (though more abstract) points of view from which to develop the science of psychology.—I am, etc.,

London, W.1. WILLIAM BROWN.

SIR,—Dr. F. M. R. Walshe's Linacre Lecture (August 12, p. 379) contains much wisdom, and many, including myself, will agree with most of what he says. It is a pity, however, that in such a thoughtful lecture he should have embarked upon the subject of methodology in psychiatry with so little circumspection. In the course of his argument he upbraids medical psychologists for their blindness in claiming to use the scientific method of natural science. He exonerates those "sage medical psychologists" who, using physical methods, know them to be empirical. He does not, by the way, specify which physical methods. Apparently he is thinking mainly of leucotomy. All other psychiatrists, in their anxiety to be "scientific," are thought to be actuated by unconscious yearnings to acquire some sort of academic prestige within the world of ordered knowledge. He anticipates that his remarks will set off rhetorical land-mines, but, undismayed, he proceeds upon his hazardous way. The expectation of rhetorical land-mines will hardly be realized. Dr. Walshe is not opening up new ground. It is true that the Goulstonian Lecturer of 1926 supported the claim that psychiatry was within the ambit of natural science and used its method. But other psychiatrists disputed this claim, as they had done earlier. Dr. Walshe is apparently unaware of their contributions upon this somewhat ancient theme.

Some psychiatrists—by no means all—have clear ideas upon the subject of methodology, and their number is not limited to those who employ physical methods—in his use of this term. Dr. Walshe may be glad to know that within psychiatry itself there are those (for example, certain psychotherapists) who have repudiated the claim that the only acceptable method in psychiatric practice is that of the natural sciences.—I am, etc.,

London, W.1. E. A. BENNET.

Inflammability of Ethyl Chloride

SIR,—Having read the instructive article on "Poisoning due to Inhalation of Methyl Bromide," by Drs. A. C. MacDonald, I. C. Monro, and G. I. Scott, in the *Journal* of August 19 (p. 441), I feel that their remark, "Like chloroform, ethyl chloride, and carbon tetrachloride it is not inflammable," should not pass without comment. Ethyl chloride is, surely, highly inflammable, burning, in fact, with a greenish flame. When mixed with 5–15% of air, it is actually explosive (*B.P.C.*, 1949). Few anaesthetists would feel justified in using "open E.C." in the presence of the diathermy, and disaster might result if one attempted to put out a fire with a bottle of ethyl chloride.—I am, etc.,

London, S.E.1. T. H. S. BURNS.

SIR,—Drs. MacDonald, Monro, and Scott state in their article on methyl bromide poisoning in your issue of August 19 (p. 441) that ethyl chloride is not inflammable. A surgeon who was about to remove a wart from my abdomen by means of cautery and local anaesthesia, with ethyl chloride spray as the anaesthetic, was also of this opinion. I can assure Drs. MacDonald, Monro, and Scott, with considerable warmth, that ethyl chloride is very much inflammable. The wart was undoubtedly removed, but the surgeon and I spent a very exhilarating few seconds extinguishing the resulting conflagration on my abdomen.

Fluid ethyl chloride can easily be ignited by the pea flame of a bunsen, but not, I believe, by a dull red fire. It was the latter fact that had led to my surgeon's belief.—I am, etc.,

Liverpool. H. E. VICKERS.

An Interesting Advertisement

SIR,—The grave shortage of psychiatric social workers is now well known, and makes discussions of improved mental health services, both preventive and therapeutic, largely academic. All with knowledge of the problem are agreed that the present salary scale is inadequate for workers who bear considerable responsibilities, and whose training lasts at least three years. That it is wholly out of relation to current rates is illustrated by a recent county council advertisement for mental health workers which reads as follows:

". . . Preference will be given to duly qualified Psychiatric Social Workers or candidates with a Diploma or Certificate in Social Science, and if so qualified the salary will be £370 by £20 to £530 per annum, commencing according to experience. For unqualified persons the salary would be £480 by £15 to £525 per annum."

This means that the unqualified start at £110 per annum higher than the qualified. Is it surprising that for several years past insufficient suitable candidates have come forward to fill training vacancies?—We are, etc.,

London, W.1. JOHN D. SUTHERLAND.
JOHN BOWLBY.

Chlorinated Swimming-pools and Poliomyelitis

SIR,—In recent announcements concerning poliomyelitis it has been stated that in certain places the swimming-pools were to be closed. This seems prudent. I have only three or four times swum in such places, but on each occasion I was immediately aware of an intense nasal irritation set up by the chlorinated water. Since then I have always believed that this is probably one important factor which encourages the spread of poliomyelitis, owing, I think, to the chlorine being ineffective as an agent for the destruction of the virus, but being present in quite sufficient concentration to disturb the normal resistance of the nasal mucosa and thus lay open an easy portal of entry, through the cribriform plate of the ethmoid and elsewhere, through the mucosa. Non-chlorinated water may be unpleasant to bathe in, but it is not necessarily dangerous.

I well remember the Merton Street Bath at Oxford. This was reserved for members of the University for bathing and for water-polo matches, but we boys of Magdalen College schools were allowed to use it, and we went there every evening in the summer when we were not swimming in the Cherwell. In Eights Week the bath was crammed with those who, having run and sweated on the tow-path, wished to cool down before going into Hall. There were no showers for a preliminary rinse; everybody just pulled off his zephyr and shorts and went in. The content of bacteria and other low forms of life must have been prodigious, for the water was only changed two or three times in the term of eight weeks, the signal for this being the impossibility of seeing the bottom—an event which occurred quite suddenly and was due, I suppose, to the rapid growth of some mould. Admittedly, poliomyelitis was uncommon in those days. None the less, it is of interest that, despite the filth of the water—of which, of course, we took no heed—I do not remember any case of otitis media among us, and the school was then a small one. During my five years as a schoolboy I am certain there was never a case of mastoid suppuration, nor, so far as I am aware, was there any unusual incidence of serious nasal or eye disease.

The nose is designed to probe into strange places and to be assailed in a variety of ways, but it will look after itself. I think it is fair to say that to wash it out with the attractive-looking water of a chlorinated swimming-pool is to invite disaster.—I am, etc.,

London, W.1. R. OGIER WARD.

The Internal Spermatic Fascia

SIR,—I would like to make some comments on Mr. C. Brun's article (August 19, p. 443). First, I think he will agree that (1) a stretched internal ring means a prolapsed cord and a defective muscular (valvular) mechanism; (2) there is no new surgical procedure which will completely restore a defective muscle action; (3) sutures in fascia, such as the transversalis fascia, cannot be regarded as a preventive against further stretching. Secondly, I cannot help feeling that if he agrees that the essential weakness of any well-developed inguinal hernia lies in the posterior wall of the canal, then buttressing of this wall by obliteration of the gap between the inner part of the

conjoined tendon and the inguinal ligament should be continued laterally, using either continuous or interrupted sutures. In this way the size of the internal ring is constricted until the new posterior wall fits snugly up to the forefinger, pressing the cord and ring outwards and backwards. Thirdly, I see no point in visually defining the internal ring in indirect herniae, as it can be palpated so much more easily, and there is no real hindrance to the action of displacing the cord outwards by finger pressure. The sutures used in the outer part of the new posterior wall should of course pick up the stretched fibres of the internal ring, in passing from the internal oblique muscle to the inguinal ligament.—I am, etc.,

Peterborough. D. W. BRACEY.

Domiciliary Treatment of Tuberculosis

SIR,—I feel I must express my sympathy for the patients who, under Dr. Crosbie Walsh's care (*Journal*, August 26, p. 525), are presumably denied the benefits of attending the local chest clinic. For his information and that of any other practitioners who may feel that they should "by-pass the tuberculosis officer," it may perhaps be well to enumerate a short selection of the services provided at chest clinics.

These include:

(1) Assessment of the significance of radiological appearances by the comparison of comparable films by physicians continuously confronted with the hazards and difficulties of this aspect of diagnosis.

(2) Advice given by physicians and health visitors versed in the special problems associated with these long-term cases.

(3) Arrangements for prompt financial assistance as afforded by the present scale of Government allowances.

(4) Arrangement of home-helps, boarding-out of children, special schools, recommendations for suitable jobs, and a hundred other vital forms of social assistance.

(5) Examination of contacts—primarily a radiological technique.

(6) Recommendation for sanatorium, surgical treatment, etc., which must in the vast majority of cases be done through these clinics.

(7) The controlled maintenance of adequate collapse therapy.

It is difficult to see how Dr. Crosbie Walsh can claim to provide a comparable form of assistance to his patients in these matters, quite apart from being able to assess the indications for streptomycin, etc., the hazards of which are being continuously stressed.[1,2]

In our area, in which we enjoy a full degree of co-operation with general practitioners,[3] we still get at least one new case a month in which valuable weeks or months have been wasted by trying to arrive at a diagnosis without reference to the chest clinic.

Finally, as the question of co-operation between general practitioner and chest clinic has been raised, may I put in a plea for careful history-taking, with special reference to time factors, in all cases who attend the doctor's surgery with a condition which might prove to be pulmonary tuberculosis? The history is the important factor in the early diagnosis of pulmonary tuberculosis, and the practitioner gets this first.—I am, etc.,

Hounslow. B. MEYER.

REFERENCES

1 *British Medical Journal*, 1949, **1**, 280.
2 McCoy, Herbert I., *Amer. Rev. Tuberc.*, 1950, **62**, 223.
3 Heller, R., *Tubercle, Lond.*, 1949, **30**, 204.

SIR,—The last thing I desire is for this correspondence to degenerate into a war between tuberculosis officers on the one hand and general practitioners on the other, because I have always believed that we must work together. However, I feel that the letter from Dr. R. Crosbie Walsh (August 26, p. 525) calls for comment.

I desire that every tuberculous patient should have the skilled treatment necessary in his particular case. I do believe that a tuberculosis officer who keeps himself up-to-date by working in close co-operation with the tuberculosis hospital and thoracic surgery centre is better qualified to assess cases for chemotherapy than a general practitioner. The analogy made between tuberculous cases suitable for streptomycin and puerperal sepsis cases requiring penicillin does not stand scrutiny. We all know that puerperal sepsis cases require penicillin, but on the other hand all cases of tuberculosis are not suitable for streptomycin. Furthermore, Dr. Walsh must have little idea of the respective functions of a medical officer of health and a tuberculosis officer if he does not know that the former is an administrator, not concerned with treatment, whereas the latter is a clinician.

I agree that it is the responsibility of the general practitioner to treat his tuberculous patients as well as others, but I think that treatment should be discussed with the tuberculosis officer, who should know what the future plan of treatment is likely to be and whether the suggested treatment will be beneficial or otherwise. Dr. Walsh appears to have been most unfortunate in his dealings with his local tuberculosis clinic, for I am sure that most tuberculosis officers, overworked though many of them are, are only too pleased to discuss their cases personally with the general practitioner if this be desired, and I think they all try to keep him informed by letter of any changes in *x*-ray or other findings.

The limited facilities placed at our disposal in the past by some local authorities may have caused some tuberculosis officers to be less helpful to the general practitioner than they might have been. It is to be hoped that all chest clinics will soon be adequately equipped and staffed to deal properly with the tuberculous population of their areas.—I am, etc.,

Liverpool, 18. WILLIAM D. GRAY.

SIR,—With great surprise I read Dr. Walsh's reply and criticism (*Journal*, August 26, p. 525). Dr. Walsh most likely has been very lucky to get a "teaching hospital chest physician" to deal with his difficult cases arising out of the antibiotic treatment of tuberculosis. It would be a really sad day when we see the general practitioners, who are the main pillars of an efficient medical service, by-passing any branches of specialized medicine. But I want to ask him a few questions.

What procedure does a provincial doctor take when requiring institutional treatment for tuberculous patients? What percentage of his open tuberculous patients have been admitted to teaching hospitals? (We ought to remember there is only one Brompton Hospital in the whole country.) I am only very new in the tuberculosis service of the country, but my short experience shows that in dealing with tuberculosis, which not only requires curative treatment but entails massive social and economic adjustments, proper co-operation between general practitioners, chest physicians, and tuberculosis officers must be maintained on the highest level.—I am, etc.,

Manchester, 13. S. S. CHATTERJEE.

The Case for Abortion

SIR,—It will surely be the general view among your readers that Mr. Albert Davis and yourself have done a considerable service in publishing his "Report on 2,665 Cases of Abortion" (*Journal*, July 15). The report is defined as intended "to determine the relative merits of active and passive treatment in cases of incomplete abortion," and within these terms adds considerably to our knowledge. One cannot help feeling, however, that the material provided among the incidental findings raises farther-reaching questions. I trust a comment may be permitted along these lines.

Of the cases generally (the great majority of which were those of attempted illegal abortion among married women) it was noted that in almost 1 in 10 there was a history of previous abortion. Also, that the abortions had been induced either medicinally or by douching. These facts lead to two conclusions: (1) that women in the relatively favourable state of legal marriage had been brought by unwanted pregnancy to such mental distress that in 253 cases they were willing to attempt abortion again, *after having had the experience*, which argues a certain desperation; (2) that these women must already have been in a very poor state of physical health if "female pills," purgatives, or douches could produce effect. Upon the healthy system they are quite ineffective; but for which fact very many people living to-day would not have entered this world.

If it is a fact that psychological health affects physical health, if to endure humiliation, pain, and danger of death rather than

fulfil a natural function implies some degree of psychological sickness, then there must be a case for close consideration of psychological and environmental factors as they affect health when the decision for or against the termination of a pregnancy is made. This decision should be neither in the hands of the mother, who cannot see beyond her immediate situation or understand all the factors involved, nor in the hands of the gynaecological specialist, who cannot be expected to be fully informed regarding psychological and environmental factors and their probable results, nor in the hands of the psychological practitioner alone, since he needs friendly conference with both the gynaecological specialist and most particularly with the general practitioner, the key-man immediately in touch with the personality and background of the patient.

Mr. Davis gives, as a permissible indication for termination of pregnancy, "*gross* physical disease." This requires elaboration. What, in fact, is "gross" physical disease? Has the mother to have both feet in the grave before relief is afforded her? Mr. Davis states: "The indications were those usually accepted as necessary for therapeutic induction, with the possible exception of pulmonary tuberculosis, *but the difficulty of obtaining suitable sanatorium accommodation for these patients is usually an overriding factor*" (my italics).

This in fact means that in such circumstances environmental factors—indeed, economic factors—were taken into account, in so far as they would in all likelihood eventually render the mother unfit to give birth. Upon this basis, is it unreasonable to conclude that, where environmental factors will cause such tremendous stress as to affect mental health to the extent of rendering a mother unfit to give birth, relief should also be indicated? Yet Mr. Davis notes, "Several patients with temporary mental instability were referred by psychiatrists, but this was invariably transient, the result of unwanted pregnancy, and interruption was refused."

This must inevitably prompt the question whether the after-histories of such patients are available over a long period of years. In the experience of every psychological practitioner (not merely in theory) it is found that temporary mental instability never results only from an immediate stress. The unwanted pregnancy is not the cause of the temporary mental instability, it is only the precipitating factor. The original cause usually lies many years back. Since the true cause of the mental instability remains untouched, let a new stress arise years later (and in the case of the unmarried mother in poor circumstances, how many chances there are that this will happen), and the mental instability will be back again *in more acute form*. Unless a secure and not greatly troubled future can be guaranteed for the woman suffering temporary mental instability as the result of an unwanted pregnancy, or unless a cure is effected by prolonged analytical treatment, then she is almost bound to relapse at the next practical crisis of her life, and her child, too, will suffer. Therefore psychological treatment should always be given as the natural accompaniment of refusal of termination.

When a woman is found to be suffering from temporary mental instability, precipitated by unwanted pregnancy, the psychiatric practitioner must (with the aid of the family doctor) endeavour to assess the environmental factors, together, of course, with those "inner" factors upon which the pregnancy has, from the practical viewpoint, acted only as the precipitating agent. These may include the unmarried status of the mother, the overburdened lot of the mother of several children, extreme poverty, lack of housing accommodation, unhappy marriage, and so on. No one of these things could by itself ever be accepted as an indication for termination. They may, however, singly or in combination, constitute that final stress which (added to other "inner" factors) might push a woman over the edge of sanity.

For a married woman who has already been through the ghastly experience to attempt second (and even more) abortions argues *ipso facto* a degree of mental instability for the time being (and of latent instability which may be permanent) sufficient to justify examination of her case.

Mr. Davis notes (and the experience of most of us, as well as the statistical evidence, will confirm) that "the complication rate is much higher in illegitimate abortions. In the present series of 315 unmarried women severe complications—gross haemorrhage, virulent infection, pelvic abscess, etc.—were present in 43 (14%) of the cases, while the corresponding figure for the 2,350 married patients was only 6%. . . . The most likely explanation lies in a combination of several factors—the inexperience of these girls, their isolation, and the desperate nature of their predicament." Here, if more is needed, is sure confirmation of the fact that mental factors exert deep influence upon physical health.

It is not, again, suggested that the fact that a girl is unmarried is *in itself* an indication for termination, or should ever be so; or that the decision should lie in her own hands. The proposal is rather that, when the decision is taken by gynaecological specialist, psychiatrist, and family doctor in consultation, the greater actual physical and mental risks run by the unmarried mother should be borne in mind—in precisely the same way that the risks run by the unhospitalized phthisic expectant mother are borne in mind by Mr. Davis.

The note that only 1% of the cases mentioned in the report were instances of therapeutic abortion leads one to wonder whether there is not some connexion between this figure and the far greater (and frightening) figure of 90% of cases considered to have been improperly induced. This appalling figure should make us begin to realize the nature of our individual responsibility when we refused consideration to such a request. Surely of those 2,400 cases there must have been a number of individual instances where there were in fact legal grounds for termination?

If not only the frequency of abortion and the state of physical health of individual patients in these cases, but also some details of their background, could be obtained, a great new light would be thrown upon this whole subject. The following heads would cover some of the most pertinent points: the precise reason driving the mother to the desperate expedient of illegal abortion; existing number of children; relationship between husband and wife (or between unmarried girl and her parents, and the man responsible); and family income and accommodation. No doubt more could be added.

I myself hope one day to publish the results of cases (of a different section of society from that of Mr. Davis's series) considered on psychological grounds; a certain number where the pregnancies were terminated and a larger number where the patient was made to understand the rightness of continuing to full term.—I am, etc.,

London, W.1. EUSTACE CHESSER.

Abortion

SIR,—There is a good deal to criticize in Albert Davis's article on abortion in the *Journal* (July 15, p. 123). May I consider a few points?

Under "Civil State" he writes, "Of the 2,665 women, 2,350 were married, 303 were single, and 12 widows. This is in accord with McIlroy's (1929) report that abortion is most frequent in the married." Must he not also consider the relative frequency of married, single, and widowed women in the general population?

I am quite incapable of believing that of 2,665 patients only 13 had a retroverted uterus. I suggest with some confidence that many of the case-papers lacked a specific note on the position of the uterus and that there must have been far more in retroversion. Mr. Davis writes: "In nine cases the patient had aborted incompletely before admission. The uterus was replaced in the remainder, but in only one case was this *successful in producing continuation of the pregnancy*" (italics mine). I believe that if you wish a patient with a retroverted uterus to miscarry, the simplest plan is to manipulate her uterus into anteversion.

As there were four cases of impaction and only two of retention of urine, I should be interested to know what Mr. Davis means by impaction of a retroverted uterus without retention: it is not a condition with which I am familiar.

I am completely floored by the logic of the last two lines of this paragraph on retroversion. The fact that of 13 patients admitted for abortion 9 were incomplete on admission, and 3 more aborted after the uterus was manipulated, does not prove

to anybody "the difficulty of preserving such pregnancies": it proves nothing. Every gynaecologist of experience has seen many patients with a retroverted uterus who have threatened to abort and then gone on to term.

Under "peritonitis" on page 128 one successful hysterectomy leads him to conclude that "there is a definite though necessarily limited indication for its use in post-abortal peritonitis." The conclusion may possibly be right, but it is not justified by the evidence given,—I am, etc.,

Leeds, 2. ANDREW M. CLAYE.

Haemorrhage from Peptic Ulcer

SIR,—Sir Robert Hutchison's suggestion that "every peptic ulcer once established as chronic be operated on in the cold" (August 19, p. 459) is utopian rather than practical and fails to take into account several obvious difficulties:

(*a*) A local practitioner discussing the incidence of peptic ulcer stated that he had in his practice approximately 100 patients "of duodenal type," of whom not an inconsiderable number would merit surgical consideration. The North-eastern Region (Scotland) area serves a population of roughly 400,000, which by simple computation would yield some 16,000 duodenal dyspeptics. Assuming that only 1 in 20 be "definitely established as chronic"—and such assumption cannot be an overestimation—the waiting-list for gastrectomy would be 800.

(*b*) The practising surgeon and physician must have encountered perforations and haematemeses which occur unheralded in a clinically silent duodenum. Thus, even although the established chronics have been dealt with, a fruitful source of perforation and haematemesis remains.

(*c*) Since 1945 the number of beds available for general surgery has decreased by virtue of the demands of thoracic, neurosurgical, and vascular clinics. The National Health Service too, far from increasing the accommodation, has meant a reduction in the number of available beds in this area.

Hence, in this area at least, in which Drs. Needham and McConachie (July 15, p. 133) have compiled their recent statistics, any attempt to forestall perforation and haematemesis by mass surgery on the established chronic ulcer would inevitably fail.—I am, etc.,

Aberdeen. W. MICHIE.

SIR,—Having been brought up since childhood to respect the name and opinions of Sir Robert Hutchison I was delighted to read his letter under the above heading in the *Journal* of August 19 (p. 459) expressing so succinctly the beliefs of many surgeons. Twenty-five years ago gastro-jejunostomy held sway in the treatment of even the most unsuitable types of peptic ulcer, and the mortality of gastrectomy was forbiddingly high except in the hands of one or two pioneer experts. In recent years surgeons working on the unpromising material provided by the failures of medical treatment, the half-starved, the exsanguinated, and the chronically enfeebled have succeeded in restoring a large proportion of patients to a decent level of digestive and general good health with a small operative mortality. Nevertheless, we are still not having ulcer dyspeptics referred for surgical treatment until disaster is at hand or has actually occurred. There then ensues a period fraught with anxiety and alarm for the patient, the relatives, and all concerned; during these hours the question of an emergency operation must be considered, continuous transfusion and constant nursing vigil add to the strain on all until, only too often, the dismal revelations of the post-mortem room humiliate us with the information that the patient must have been living with the threat of a lethal haemorrhage from a chronic peptic ulcer for many years. Few would question the advisability of operating on an inguinal hernia before strangulation occurs; why then should the profession accept the risks of haemorrhage, perforation, or malignant change in a chronic peptic ulcer with equanimity?

In conclusion I would strongly endorse Sir Robert Hutchison's appeal not only as a measure that will save the patient chronic invalidism and a constant threat of sudden death, but as a measure that will save the hospital service hundreds of beds, the nursing profession untold hard work, and the transfusion service gallons of blood.—I am, etc.,

Weymouth D. J. ROSS STEEN.

Extreme Hyperpyrexia with Recovery

SIR,—I would bring the following case to your notice as illustrating the tenacity of life among the Chinese.

The patient, a rather emaciated Chinese aged 67, came under my care complaining of right-sided abdominal pain and constipation of four days' duration. He had not vomited, and there was no history of preceding dyspepsia or jaundice, or of previous attacks. On examination his condition was good (pulse 100, temperature 98° F. (36.7° C.)). The whole of the right side of the abdomen was rigid, and he placed the site of maximum pain and tenderness just to the right of his umbilicus. The conjunctivae were pale, and the patient was anaemic. A diagnosis of acute cholecystitis, ? acute appendicitis, was made.

The abdomen was opened through a right paramedian incision and the gall-bladder found to be acutely inflamed and full of small stones. The sounder courses of closure or cholecystostomy were discarded, and cholecystectomy was embarked upon; this was accomplished with some difficulty and the loss of a modicum of blood by the patient. On leaving the theatre his condition was still fairly good, the pulse being 130 but of good volume. One and a half pints (840 ml.) of saline was given intravenously during the next three hours.

After this time it was decided to give him blood, and one pint (560 ml.) Group B was obtained from a donor and cross-matched. After half a pint had been given at about 20 drops per minute the patient began to have rigors. The transfusion was stopped, but the rigors continued and became worse. After half an hour his temperature had risen to 107° F. (41.7° C.) and his pulse to 150, being barely perceptible. Nikethamide 1 ml. was given and cold sponging commenced. During the next half-hour the patient became worse. The pulse could not be felt anywhere, the breathing was shallow and laboured, and the limbs cold and wet. The axillary temperature rose to approximately 112.5° F. (44.7° C.). (The thermometer scale stopped at 110 degrees, but by producing the marking it appeared that the reading lay midway between 112 and 113. This was checked by three readings in the next five minutes.) Quinine 15 gr. (1 mg.) was given intravenously together with a further 1 ml. of nikethamide, which was continued hourly. The cold sponging was continued. The patient now appeared moribund. However, an hour later he improved slightly, the pulse being just perceptible (150), and the temperature 101° F. (38.3° C.). The improvement continued, and by the next morning he was conscious and taking fluids by mouth, with a pulse of 120 of fair volume and temperature of 100.5° F. (38° C.). His subsequent convalescence was uneventful. For three days his temperature remained about 100° F., after which it became normal. He began to sit up on the fifth day and to walk about on the tenth. It would seem that he has suffered no permanent harm from his pyrexia.

I am at a loss to account for his somewhat alarming rise in temperature. The strife and bloodshed occurring in this particular part of the Empire necessitate frequent massive blood transfusions, but we are not accustomed to meet with such reactions. The grouping and cross-matching were properly carried out and the apparatus was clean and sterile. The patient showed no evidence of chronic malaria.

I am grateful for permission to publish this case.—I am, etc.,

Malaya. J. T. ROWLING, Lieut., R A M C.

Sulphonamide Therapy

SIR,—Professor D. M. Dunlop (August 12, p. 408) made no mention of sulphanilamide, of which I happen to have a stock in tablet, powder, and cream form. Nor did he mention the application of sulphonamides in the treatment of burns. Could he, moreover, express opinion as to the value, if any, of a couple of doses (2 g. each) of, say, sulphanilamide as a prophylaxis of gonorrhoea on "the morning after"? Such information would be much appreciated.—I am, etc.,

H.M.T.S. "Monarch" J. L. BARFORD, Ship Surgeon.

Poliomyelitis and Inoculations

SIR,—The incidence of muscular paralysis, confined to the inoculated limbs, which is described in Dr. J. Newcombe's letter (*Journal*, August 12, p. 416) is a classic example of the type of case which still startles medical opinion. Such cases, however, offer a good opportunity for an analysis, because here we are at least dealing with some known factors, similar to those we encounter with the inoculation of vaccines, or antibiotics, or sera. But so far the factor of an adjuvant, apart from the

needle, has not been taken into consideration, whether it is the micro-organisms present in the vaccine or the micro-organisms causing infection. This factor of infection, for which Dr. Newcombe injected penicillin, was completely ignored as an additional causative agent, although the febrile reaction and boil formation were due to some of the staphylococcal series.

Trauma can always be regarded as a precipitating factor for an entry of the virus, since it exposes the muscle motor-end plates to an open attack at the myo-neural junctions. In the case of the neurotropic virus, such an entry is a prerequisite for it to be able to exert its pathogenic activities.

But there are also chemical changes taking place as a result of trauma: muscle tissue is hydrolysed, in consequence of which there will be released a series of enzymes, like myosin ATP-ase, carboxylase, phosphatases, and also adenosine compounds like ATP, ADP, or creatine phosphate. Also we find liberated a series of ions, such as Ca, Mg, K, P, and organic acids, resulting in a gross shift of the *p*H and ionic balance. Micro-organisms contain large amounts of nucleic acids in combination with proteins. When infection as well as trauma is present some of the micro-organisms will die or be disintegrated under the influence of antibiotics and their nucleoproteins released into inflammatory tissue, still physiologically active. The best comparison one can offer is with Griffith's discovery of the transformation of one type of pneumococcus into another type by bringing into contact, *in vivo* or *in vitro*, the living form "R" variant of the type to be transformed with the heat-killed form "S." Avery and McCarty and MacLeod isolated this transforming agent, which is a sodium-desoxyribonucleic acid.

I quite agree that these are complex factors, but without an understanding of the biochemical principles involved the problem of poliomyelitis can hardly be solved.—I am, etc.,

Hayes, Kent. L. RETI.

But Was it Poliomyelitis?

SIR,—Last year when I was in Brigg (Lincs) I had some cases of children febrile and perhaps dragging a leg or not using an arm which seemed painful if moved. I used to give 1 mega unit of penicillin. This—or perhaps three subsequent doses of ½ mega unit daily—cleared the condition.

It may have been mild poliomyelitis: I did not diagnose it at the time, being satisfied if the child was well again, and all the cases were well with this treatment. Therefore I think penicillin in huge doses given *early* in any febrile condition in any district where poliomyelitis is known to be is justified. No time should be lost awaiting results of swabs.—I am, etc.,

Keighley. FLORENCE M. E. DAVIES.

Treatment of Acute Yellow Atrophy

SIR,—On p. 214 of the *Journal* (July 22) an account is given of the meeting of the North of England Obstetrical and Gynaecological Society held at Newcastle-upon-Tyne on Friday, June 2, 1950. I gather that you have been given an incorrect description of the infusion I used for treatment of yellow atrophy of the liver. The quantity of nicotinamide should be 150 mg. and the infusion should also contain potassium chloride. It is correct to state that three pints of the infusion are given daily, but this is followed, not by a pint of saline, but by a pint of plasma to which vitamins have been added. The treatment is actually more complicated than would be inferred from reading the report and is given in detail in the paper which is awaiting publication in your *Journal*.

At the meeting, Mr. Stabler made it very clear that he was showing these cases solely because of their obstetric interest, and that they were included in a series of five cases to be reported upon by myself.—I am, etc.,

Newcastle-upon-Tyne. A. L. LATNER.

Osteoarthritis

SIR,—Some of the detail in Dr. C. W. Buckley's Refresher Course paper (June 17, p. 1415) is a strong stimulus to criticism.

Trauma can hardly be an important cause of osteoarthritis, as the condition is common in persons whose occupation is of a sedentary nature. It also occurs in persons who have abstained from exertion as far as possible throughout their lives on account of cardiac lesions or other reasons. The effect of injuries on joints is well known and often loosely termed "osteoarthritis," but the condition is not the same. Massage is recommended to relieve muscle spasm. Surely the existence of such an unusual feature as muscle spasm calls for a review of the diagnosis? If surgery is left till pain is severe and deformity serious the results are certainly likely to be disappointing, and if as stated the patient remains in hospital in splints for a long period failure is almost certain.

Osteoarthritis of the hip is more commonly bilateral than unilateral, though commonly symptoms commence first on one side. The alternatives to cup arthroplasty of the hip-joint—namely, arthrodesis and osteotomy—are not mentioned, and manipulation under anaesthesia, which is a popular method of treatment of osteoarthritic joints and spondylitis, is not discussed.

Patients are justified in objecting to wearing callipers or Marsh knee cages. If they need them they could probably be served better by surgery.

—I am, etc.,

Melbourne, Australia. FRANKLYN STONHAM.

Penicillin and the Skin

SIR,—Professor L. P. Garrod in his article on "Administration of Penicillin" (*Journal*, August 19, p. 453) states that it has "all the properties of an ideal antiseptic . . . without doing the slightest harm to tissue." During the war, however, as well as later, I have had the opportunity to observe that skin-grafts to which penicillin had been applied disappeared rapidly and with distressing regularity. I have seen ulcers of many months' standing. Soon after the appearance of a small lesion the patient had been applying penicillin ointment for several weeks and months. Remembering the resorption of skin-grafts, I ordered the discontinuation of the ointment. The ulcers disappeared under a dry dressing within a few days.—I am, etc.,

London, S.W.3. E. F. BLUMBERG.

Strangulated Hernia in Infants

SIR,—On December 23, 1949, a 21-day-old African male was admitted to hospital at 7.30 p.m. suffering from a strangulated right inguinal hernia. This had occurred the previous night, about 20 hours earlier. The bowels had not been open for 24 hours, and the abdomen was slightly distended. The child had vomited six times and there was a tense irreducible swelling in the right inguinal region. The temperature was 98° F. (36.7° C.) and the pulse rate 142.

No anaesthetic was used for the operation: the child was crucified on splints, and the anaesthetist who was standing by kept the child quiet by letting it suck his little finger. At operation there was a loop of small intestine in the sac, in good condition. The inguinal ring was then enlarged, and attempts were made to replace the gut. Owing to straining, this was very difficult, as the intestines were constantly being forced out. It was finally accomplished at the end of 45 minutes. While the incised ring was being repaired there was a flood of urine all over the field of operation. The source of the puncture in the bladder could not be traced, so the area of leakage was oversewn. The inner surfaces of the sac were sewn together, and the wound closed. As the operation had now taken 60 minutes, the skin was closed with a continuous suture to save time.

There was no post-operative leakage of urine from the wound, but it broke down on the fifth day, partly as the result of the mother enthusiastically bathing the child and pulling off the "elastoplast" dressing. The skin suture came away with the dressing. The gaping skin wound was treated with eusol, and healed at the end of 26 days.

Immediately following operation the temperature rose to 101° F. (38.3° C.) and the pulse increased to 160, but the temperature had returned to normal next day and thereafter never rose above 98.6° F. (37° C.). Post-operative treatment consisted of penicillin 25,000 units three-hourly for six doses, and pot. brom. 1 gr. (65 mg.) p.r.n. The child continued to suckle normally, and put on weight. He was discharged well on the twenty-sixth day, and returned home eight miles by canoe, the way he had come.

Three months previously an African baby of 9 months was admitted with a tense right scrotal swelling of three days' duration, a distended abdomen, and vomiting. The temperature was 102° F. (38.9° C.) and the pulse rate 154. An operation was performed under general anaesthetic. There was an excess of fluid in the sac, and the loop of the small intestine was very

congested, but viable. The ring was incised and the intestine replaced. The ring was repaired and the neck of the sac closed. A drainage tube was placed in the scrotum. Post-operative treatment was penicillin 100,000 units, followed by the treatment as above. The temperature and pulse were normal by the third day. The child suffered no inconvenience, and was discharged cured on the thirteenth day.

I am grateful to the Director of Medical Services, Gold Coast, for permission to publish this report.—I am, etc.,

Gold Coast. M. P. BROWNE.

Damage to the Antrum During Dental Extraction

SIR,—The maxillary antrum is vulnerable during extraction of a lone premolar or molar tooth with alveolar atrophy around it. The danger is not at all obvious to the inexperienced. First, the tooth may shoot up into the antrum. In such case a snare is a suitable instrument with which to effect delivery. Secondly, part of the antral floor may come away with the tooth, leaving a permanent oro-antral fistula. Thirdly, an ill-advised plastic operation has the effect that, when the patient eats, saliva drips from the nose. (Such fistulae have been established deliberately in the treatment of atrophic rhinitis.) There is a better method of closing an oro-antral fistula of this kind. A palatal flap based upon the posterior palatine foramen is reflected under a longitudinal bridge of palatal tissue and sutured to the buccal margin of the fistula. This is in accordance with the soundest principles and practice of reparative surgery, and may therefore be relied upon to put matters right again.—I am, etc.,

Huddersfield. W. O. LODGE.

Minority Crusade

SIR,—Tuberculosis is very much in the news, and this is all to the good, provided it leads on to effective measures to combat the disease. We, the undersigned, fear, however, that the calls being made for a crusade against tuberculosis may result in a big expenditure of public money without any worth-while improvement in the position. Our fear is based on two considerations: (1) no known antibiotic or therapeutic agent of low toxicity is highly effective against tuberculosis, and (2) the profession as a whole closes its eyes to what is probably the main cause of our failure to get rid of tuberculosis—namely, our failure to get rid of tobacco.

In a high proportion of cases—about 60%, we estimate—pulmonary tuberculosis is complicated by tobacco smoking (tobacco smoking is a drug addiction, a specific disease). Tobacco smoking violates almost every principle in the treatment of pulmonary tuberculosis—fresh air, immobilization of diseased lung (smoking gives rise to coughing, the activity which above all others disturbs healing and starts off haemorrhages; it also spreads infection), comfortable economic circumstances (smoking is expensive and leaves less money for food, housing, leisure, etc.), and good nutrition (almost everyone who gives up smoking puts on weight, often measurable in stones rather than pounds in a few months, and this is done without resting or "stuffing" in a sanatorium; the increase in weight is accompanied as a rule by increase in well-being). Can it therefore be doubted that smoking aggravates the course of pulmonary tuberculosis in a degree dependent in the main on the consumption of tobacco and the type of smoking? The importance of this lies in the fact that tobacco smoking, unlike pulmonary tuberculosis, is readily preventable and curable. It is no more difficult to prevent than opium smoking.

The principal obstacle in the way of preventing and curing tobacco smoking is, in our view, its prevalence among medical men and women. Nicotinism in common with other drug addictions is characterized by subtle psychopathological changes. Addicts of tobacco (and of other drugs) are deluded as a rule about matters concerning their drug; about, for example, its virtual harmlessness and the reality and importance of the contribution it makes to their happiness. So fixed oftentimes are these delusions that many addicts (including medical addicts) are quite inaccessible to logic on the subject and merely project on to those who seek to undeceive them their own unconscious disturbance of judgment, dubbing them cranks or fanatics. Even those who say they are convinced about the harmfulness of tobacco smoking are often unable or unwilling to express this conviction in their actions.

Although getting rid of tobacco would not completely solve the tuberculosis problem it would be a rational and, in our view, an important step in the right direction. The harm caused by tobacco smoking is by no means confined to its effects on pulmonary tuberculosis, and we are of the opinion that the upheaval that would be caused to our economy and mode of life by abolishing tobacco smoking would be a small price to pay for the substantial gain in the health and economy of the country that would quickly result.—We are, etc.,

Wallasey. LENNOX JOHNSTON.
F. C. MORGAN.

Johann Mikulicz-Radecki

SIR,—Sir Gordon Gordon-Taylor's tribute to the memory of Mikulicz-Radecki, "the great German [*sic*] surgeon," at the 67th Congress of the Deutsche Gesellschaft für Chirurgie (*Journal*, July 8, p. 103) prompts me to sketch briefly the life of this eminent Pole. His father Andrzej, born in Sniatyn (Poland) in 1806, came from an ancient noble family of Polish patriots which goes back to the fourteenth century. Their ancestral castle Radek (from which the name is derived) is at Osmiany. One of his ancestors was a member of the Polish royal household. Another distinguished himself so much in the battle against the Turks that the King of Poland added the cross and half-moon to the family coat of arms. In 1792 the Austrians seized the family properties of all Polish patriots, and Mikulicz's grandfather lost everything.

Mikulicz had a hard life as a student. He had to make his own way by giving piano lessons and teaching languages. After graduating in 1875 he was admitted to Billroth's clinic as *Operationzöglinge* (voluntary worker), and after the publication of his paper on rhinoscleroma he was quickly promoted. He became *Privatdozent* in 1880. Having achieved this title Mikulicz had automatically to leave the faculty. This was followed by the most tragic period of his life. The brilliant young surgeon was without a workshop, and there was no hope that as a Pole he would ever get one in Austria. Things were no better when he was ordered by the Habsburg authorities to remove the Polish eagle from his coat of arms. For two years he was at the Polyclinic, and during this time he had not done a single major operation. One can imagine his state of mind when he had to turn to general practice to support his wife and child. His Polish colleagues could not see such a talent wasted, and they invited him to take charge of what was left of the Jagiellonian surgical clinic in Cracow.

One can imagine with what joy Mikulicz received this invitation. The university clinic consisted of a few rooms on the second floor, sixteen beds in all, primitive conditions, and no funds for improvement. Obviously the Habsburgs could see no advantage in spending money on a Polish university. Mikulicz put all his zeal and energy into his work. This was the only place where he could work and show the Teutonic world what he was capable of. He lectured—in Polish, of course—and, surrounded by the love and esteem of both colleagues and students, he achieved miracles in this poor little "clinic" (a useful reminder to modern surgeons who would consider work inconceivable without teams, units, and vast "labs.").

Mikulicz was at Cracow from 1882 to 1887. As Sir Gordon relates, he was the first to operate successfully for gastric haemorrhage. This took place at Cracow in 1885, and the same year saw the publication of this case. His greatest surgical pioneer work was done during his stay at Cracow. This included lateral pharyngotomy for resection of malignant pharyngeal tumours (*Gazeta Lekarska*, 1883), osteoplastic resection of foot (*Przeglad Lekarski*, 1882), plastic nose surgery (1884), thyroidectomy (1886), surgical treatment of suppurative sinusitis (*Pamietnik Lekarski*, 1882), treatment of gangrene, intestinal resection, myomectomy, etc. While at Cracow Mikulicz published over forty original papers. By 1887 he had made famous both Cracow University and himself.

When the chair at Graz became vacant everybody thought he would get it. But he was a Pole and the place went to Wolfler. However, in 1887 he was offered the chair at Königsberg. He accepted with mixed feelings, for he was sorry to leave his Polish colleagues who had helped him so much in his hour of need. It is safe to say that without their help a great surgical genius would have been lost to the world. When Mikulicz became the recognized leader of world surgery and international honours were showered on him the Austrians felt it incumbent on them to do something also. When Mikulicz was approached on behalf of the Emperor he asked

for only one honour—permission to reinstate the Polish eagle in his coat of arms. This was granted by decree in 1899.

I am relating these few historical details to show how inaccurate Sir Gordon Gordon-Taylor is when he calls Mikulicz "the great German surgeon." He may have his own views on Mikulicz's nationality, but when speaking on behalf of the Royal Society of Medicine and the Royal College of Surgeons these facts should not be overlooked. It is again becoming fashionable to flatter the Germans, but must it be done by removing Mikulicz from the ranks of great Poles and turning him into a German ?—I am, etc.,

London, W.1. S. GALEWSKI.

POINTS FROM LETTERS

Clinical Impression versus Cold Science

Colonel W. H. CRICHTON writes: I do not presume to dispute the findings of the Medical Research Council or of Lorriman and Martin on their carefully conducted trials of antihistaminics in the common cold (*Journal*, August 19, p. 425). I do, however, feel that my own personal experience with this type of treatment which led me to arrive at a very different conclusion should be placed on record. I should explain that I am prone to get "colds in the head" about two or three times in a year, usually in spring and autumn with the change of the weather, but at other times as well if indiscreet with coverings, especially after exercise. On April 24 this year I was due to proceed to Eastbourne to attend the Congress of the R.S.I. On the 23rd at midday I was conscious of a roughness of the throat and a slight fullness in the head. By the afternoon I had begun to sneeze. By evening the symptoms of a cold in the head were clearly established. I went to bed early (9 p.m.) with a hot drink and 10 gr. aspirin—my usual remedies. The next morning (April 24) the symptoms were worse: shattering and more frequent sneezes, profuse watery discharge from the nose, eyes suffused, headache, general malaise. I took 10 gr. aspirin and stayed in bed, cancelling my departure for Eastbourne and cursing my luck at missing the congress, as my colds usually last at least a week to 10 days once they are established. For this reason I was tempted to try treatment by "anthisan," and in the late afternoon I took a tablet of 0.1 g. The effect produced was that of drowsiness and slight dizziness. I slept soundly. The following morning (25th) to my delight I was obviously much better: nose practically dry, no sneezes, general malaise gone. I stayed in bed and had a second tablet of anthisan. The effect was the same as before and I slept soundly again till lunch-time. By afternoon all symptoms had disappeared and I made arrangements to proceed to the congress the following morning, but I stayed indoors (not in bed), as the weather was exceptionally bad, with snow storms. The following morning I left for Eastbourne in the most inclement weather but feeling perfectly fit and *without* the usual aftermath of a persistent purulent nasal discharge. I had no recurrence and no unpleasant sequelae. The duration of my cold before the exhibition of anthisan was 24 hours approximately, and the symptoms were by then fully established in spite of my staying in bed and taking aspirin. A complete cure was effected with two tablets of anthisan within a further 24 hours. So impressed have I been with my own cure that I have recommended it strongly to others similarly affected since then, but I have found it necessary to insist that it is useless to expect any good results *unless the patient is prepared to go to bed* for at least 24–36 hours (maximum 48 hours). If this condition is fulfilled I am confident that a complete cure can be effected in every case.

Dr. A. J. AMBROSE (Beckenham) writes: I am not satisfied that the Research Council are 100% correct. Whereas before taking "benadryl" I was troubled with frequent colds which persisted for weeks, now, since taking at most five capsules of benadryl, my colds are of minor degree. In my own family, I found that one child responds dramatically to benadryl and two children do not. Perhaps the true summing-up would be that some people do respond and others do not. And I notice the trials the Research Council made were not with benadryl, as originally advocated by Captain Brewster.

An Adjustable Bed for Patients at Home

Mr. T. M. PROUDFOOT writes: The bed which your correspondent Dr. T. H. Gillison saw in Skye (August 26, p. 530) is a model which was manufactured about 20 years ago, and my firm, John Bell and Croyden, had exhibited such a bed in the surgical section of their business in Wigmore Street. About this time the London Clinic was being equipped, and two or three of this particular bedstead were supplied for use in the Clinic. If I recall correctly, the bedstead was manufactured in Liverpool and distributed by Messrs. Alexander and Fowler, Pembroke Place, in that city, and Mr. J. D. Gray of that firm could probably give further information.

Obituary

SIR REGINALD ST. JOHNSTON, K.C.M.G., M.R.C.S.

Sir Reginald St. Johnston, formerly Governor of the Leeward Islands, died at Eastbourne on August 29 at the age of 78.

St. Johnston was the son of a doctor, and after leaving Cheltenham College he studied medicine at Edinburgh and Birmingham. He qualified in 1905, and became house-surgeon at the Dudley Hospital. After holding clinical assistantships at St. Peter's Hospital and the Hospital for Women, he was appointed assistant medical superintendent of Lewisham Infirmary in 1907. Shortly afterwards, however, he went to Fiji and worked as a general practitioner. Almost immediately he accepted an appointment under the Government of the Colony, and, finding a useful career open to him, he obtained leave to study law and was duly called to the Bar.

During the first world war St. Johnston was at first in Fiji, but he was seconded for war service in France, where he did much medical work, both practical and administrative. He was eventually attached to the War Office for special duty and was given the rank of lieutenant-colonel. At the end of the war he served for a short period as Acting Governor of the Falkland Islands, and was then appointed in 1920 as Colonial Secretary of the Leeward Islands. On a number of occasions in the next few years he acted as Administrator of Antigua, of Dominica, and of St. Kitts and Nevis. He was made Governor of the Leeward Islands in 1929. From then until 1936, when he retired, he did much to improve social conditions in the Islands. He was created C.M.G. in 1923 and promoted to K.C.M.G. in 1931. He was the author of a number of books, including *Dream Faces, The Leeward Islands, South Sea Reminiscences, From a Colonial Governor's Notebook*, and *Strange Places and Strange Peoples.*

A. D. MACPHERSON, M.B.

Dr. Angus Duncan Macpherson, assistant medical secretary of the British Medical Association from 1904 to 1935, died in London on September 3 at the age of 79. He studied medicine at Edinburgh, Dublin, and King's College, London, and he graduated M.B., C.M. (Edinburgh) in 1897. He entered the service of the British Medical Association in 1904, when the medical secretariat in the old building in the Strand was beginning to take shape under the new constitution. During the thirty-one years Macpherson worked for the Association he gained a detailed knowledge of constitutional procedure, and this knowledge he put to good effect as secretary to the Organization Committee. He was responsible each year for the production of the B.M.A.'s annual handbook, at first called *Handbook for Recently Qualified Medical Practitioners* and later renamed *Medical Practitioners' Handbook*, and it was due to his efforts that this booklet became such an invaluable aid to the general practitioner. Many correspondents and visitors at B.M.A. headquarters will remember Macpherson's invariable courtesy and helpfulness. The sturdiness of his character was exemplified by the fact that at the age of 70, during the worst period of the last war, he took a post as a ship surgeon in the Merchant Navy.

We are indebted to Dr. Alfred Cox for the following appreciation: By the death of Angus Macpherson the Association loses a former veteran of its staff who devoted to its service the best years of his life. He was little known to most members of the Association, for the work in which

he was chiefly engaged did not take him to the Representative Meeting nor indeed much into committees.

When I joined the staff in 1908 as deputy medical secretary I found Macpherson there as the only medical assistant to Dr. (later Sir) James Smith Whitaker. But for his comparative youth and lack of experience in the then burning question of contract practice it is probable that he might have been promoted to the position I then took. He continued till he retired in 1935, having found his *métier* in work which, though little attractive to most of us, he thoroughly enjoyed. He loved the detail connected with the drafting and revision of articles and by-laws and regulations. He was the soul of accuracy and could always be relied on.

I saw him but rarely after his retirement. For a time he engaged in general practice in Chelsea, and then went on several voyages as ship surgeon. A few weeks ago I heard he was very ill and went to see him. He was suffering from malignant disease of the prostate, and I found him a mere shadow of his former self. He was obviously near his end, but I never met anybody who faced death with greater equanimity. He made no complaints and was still full of interest in the work of the Association. On this he was a mine of information, and I regret that he never committed it to writing, for his term of service covered a period of great importance.

All of us who knew anything of his domestic circumstances admired him for his striking devotion to his wife and two sisters, who lived with him. Our sympathy goes out to those he has left behind, and his memory will live with us as a good man and loyal colleague.

Dr. MATTHEW BURROW RAY, for many years senior physician to the British Red Cross Clinic for Rheumatism, died in London on July 5 at the age of 80. He studied medicine at Edinburgh University, and graduated M.B., C.M. in 1893, proceeding M.D. in the same year. He was admitted M.R.C.P.(London) in 1934. Before the first world war he held a number of appointments, and at one time he was pathologist and assistant medical officer at the West Riding Mental Hospital, assistant surgeon to the Eston Hospital, and honorary surgeon to the Harrogate Infirmary. He was a past president of the Harrogate Medical Society. He served as a colonel with the R.A.M.C. in the 1914–18 war, being A.D.M.S. of his division, the 47th (2nd London), T.A. He was awarded the D.S.O. in 1917. After the war he and the late Dr. Fortescue Fox were instrumental in establishing with the British Red Cross Society the well-known clinic which is now the Arthur Stanley Institute for Rheumatic Diseases at the Middlesex Hospital. He was the first chairman of the honorary medical committee of the Clinic, and in recognition of his services the British Red Cross Society decided that he should remain a member of the active staff as long as he wished. In fact he worked at the Clinic until it was taken over by the National Health Service and absorbed into the near-by Middlesex Hospital in 1948. He continued to act as physician and director of the department of physiotherapy at the St. Marylebone and Westminster General Dispensary. Dr. Ray was a great expert on hydrotherapy, and his knowledge of the spas of Europe was in a class by itself. He was an active and useful member of the British Medical Association, being chairman of the Marylebone Division in 1934–5. He was a representative of the Division at several Annual Meetings, and for two years he was also an officer of the Section of Physical Medicine. He served on a number of committees connected with his specialty, and he was at one time honorary treasurer of the British Association of Physical Medicine. In 1930 he gave a Chadwick lecture on "The Treatment of Rheumatism," and among his publications were books entitled *Rheumatism in General Practice* and *Hydrotherapy and Climatotherapy*. Dr. Ray was a sound clinician, a physician of the old school in the best sense. His character was exemplified by his devotion to his work and his patients. He obtained great satisfaction from his two creative hobbies—painting and carpentry. He is survived by his widow, to whom the sympathy of his friends, colleagues, and patients will be extended.

Dr. ALEXANDER CHRISTIE REID died suddenly while on holiday in Edinburgh on August 20 at the age of 76. He was educated at Aberdeen University, taking the degrees of M.A. and B.Sc. before entering on his medical studies. He graduated M.B. in 1902 and proceeded M.D. with honours in 1905. In 1913 he took the Oxford Diploma in Ophthalmology. For nearly 40 years he was honorary surgeon to the Nottingham and Midland Eye Infirmary, and for many years was consultant ophthalmic surgeon to the Kesteven county council and the Mansfield and Worksop Hospitals. He retired from active consulting practice four years ago, and for his distinguished service was appointed consulting surgeon to the Nottingham and Midland Eye Infirmary. During the 1914–18 war he served as a captain in the R.A.M.C. Dr. Reid made a study of miners' nystagmus, and to gain first-hand knowledge of working conditions went down the pit on many occasions. He always brought a clear, analytical mind to bear on any difficult problem. Apart from his professional work his interests were wide and varied. Dr. Reid will be remembered with affection and admiration by all who knew him.—G. G.-N.

Dr. FRANCIS JAMES STRONG HEANEY died at his home outside Chester on August 26 at the age of 76. He was educated at Dundask School, and later was a Stewart medical scholar at Trinity College, Dublin, where he qualified in 1901. In 1902 he proceeded M.D., and in the same year became a Fellow of the Royal College of Surgeons of Ireland. From 1907 he was a member of the Liverpool Medical Institution, where he held many offices. He was president of the Lancashire and Cheshire Branch of the B.M.A. in 1923–4, and chairman of the Liverpool Division in 1926–7. He served on the Council in 1921–4 and as a representative in the R.B. in 1920–2 and again in 1924. He also served on the Journal Committee for a year in 1921–2. Among other committees on which he served was the English and Welsh Consultants and Specialists Group Committee, 1934–40. For a number of years he was president of the Liverpool Hospital Staffs Association, and in this capacity gave his services ungrudgingly for the establishment of good professional relationships. During the war of 1914–18 Strong Heaney, who retired with the rank of Surgeon Captain, R.N.V.R., served in the R.N. hospital ships *Plassy* and *Asmirias*, and he always retained his interest in the Service. In 1919 Heaney was appointed to the Stanley Hospital at Liverpool and remained on the teaching staff of the medical school until 1946, having worked untiringly through the heavy raids which made such demands upon the hospitals in the war years. He also held appointments in Ormskirk, at the Providence Hospital, St. Helens, and in the Radium Institute. His many friends will remember Frank Strong Heaney for his great courage in tackling the difficult operative problems of cancer in the early days, for his enormous energy, and for his unfailing, cheerful, and purposeful kindliness. He was a splendid spokesman and advocate who was always loyal to his ideals, who faithfully represented the views of his colleagues, and who was logical, lucid, and determined, but pleasant and tactful withal.—C. A. W.

Dr. W. A. MILLIGAN died at his home in London on August 25 at the age of 78. He was one of the best-known medical practitioners of Mayfair and had practised there for close on fifty years. Wyndham Anstruther Milligan was the fourth son of a family of 11 children, his father being Dr. William Milligan, professor of Biblical criticism in the University of Aberdeen. His brother William became a distinguished ear, nose, and throat surgeon in Manchester. Milligan was educated in that famous seminary "The Gym," founded by the Rev. Dr. Anderson, and at Aberdeen University. He graduated M.B., C.M. in 1895, and proceeded M.D. in 1906. He became a Fellow of the Royal College of Surgeons of

Edinburgh in 1899. His sincerity, mental alertness, and directness of manner could not conceal the warm-hearted soul within. His large clientele of patients of all types had complete trust in his judgment and his diagnosis. Though busily engaged in practice, he extended his medical interests by becoming physician to the Margaret Street Hospital for Diseases of the Chest. Many patients still remember with gratitude his skill in diagnosis and his deep personal interest in their welfare. His wide view of general practice and his desire to keep himself efficient led him to become honorary gynaecologist to the Farringdon Dispensary and district surgeon to the City of London Lying-in Hospital. His special gynaecological experience merited his appointment in 1931 to a post of high responsibility as medical inspector in nullity cases coming before the High Court of Justice. He succeeded the late Dr. Gilbert Orme as chairman of the Westminster and Holborn Division of the B.M.A. in 1945. There was no more loyal or steadfast member, and none more patient or impartial ever presided over the meetings of the Division, which passed a special resolution to enable his colleagues to re-elect him unanimously as chairman for the fourth year. All his professional life he cherished a lasting affection for the Aberdeen University Club in London. He had been joint honorary secretary for many years and later vice-president, and on the death of Lord Meston in 1948 the club elected him president, a well-deserved honour. Although he was approaching his seventieth year, the second world war found him, as always, ready for whatever task might fall to him. He spent long and strenuous hours in the Home Guard, and was always on call to attend air-raid casualties at the first-aid post in Berkeley Square. The loss of his son, a naval surgeon, torpedoed in the Atlantic, caused him deep grief. During the half-century he worked in Mayfair he saw a great many changes in that area of London, but all these he viewed with equanimity, for his strong sense of service and duty never wavered. He remained at work until a few weeks ago, detaching himself with stoic calm from his own anxieties while sharing the cares of others. Dr. Milligan had been a widower for 30 years. He is survived by three sons and one daughter.

Medico-Legal

DEATH AFTER NEW DRUG

An inquest was held in June on a woman aged 67 who died after being treated with G.T.41, a drug that was being tried in the treatment of cancer. The coroner recorded a verdict of death from misadventure.[1] The woman was first admitted to hospital in July, 1945, and a radical mastectomy was performed for carcinoma of the right breast. Secondary deposits were present in the axillary nodes and surrounding tissues, and a full course of radiotherapy was given.

G.T.41 is a dimesyloxyalkane, its formula being $CH_3OSO_2(CH_2)_4SO_2OCH_3$. Though the drug is not a nitrogen mustard, its action is similar. The substance is one of a long series of nitrogen mustards and related compounds the biological properties of which have been the subject of experiment for several years. G.T.41 and other associated substances have from time to time been selected for clinical trial by oral administration in cases of advanced malignant disease, since they have an inhibitory action on the growth of certain tumours. The inhibition is not exerted against the malignant cells specifically, and various normal tissues are also affected. One of the most sensitive of these is the bone marrow. While the effect on the bone marrow can normally be controlled, in the present case agranulocytosis developed, though no other toxic side-effects had been observed during administration. The case suggests that G.T.41 is peculiar in its effects as compared with related substances which have been used clinically. It may be abnormally accumulated in the tissues, or its effects may be much less reversible than is usually the case. Its further clinical trial has been suspended.

[1] *Birmingham Post*, June 30.

Universities and Colleges

UNIVERSITY OF OXFORD

In a Congregation held on July 29 the following degrees were conferred:

D.M.—R. T. C. Pratt.

M.CH.—P. A. L. Roberts.

B.M.—W. G. Dewhurst, W. F. P. Gammie, H. Yellowlees, J. L. Godden, J. M. D. Hooper, R. S. Walsh, L. Robertson, J. G. Danaher, B. N. McQuade, R. A. Riseley-Prichard, J. H. Wilson, C. S. Pitcher, P. H. Watkins, F. B. E. Kampfner, G. E. Rousseaux, Ursula F. Rowlatt, Myrtle J. Raynor.

UNIVERSITY OF CAMBRIDGE

The following medical degrees were conferred on August 5:

M.D.—*J. R. Handforth, A. J. Rook, J. G. Benstead, G. F. Roberts.

M.B., B.CHIR.—*H. de Glanville, *J. M. Hodson, M. J. D. Newman, *K. W. Gray, *R. P. Holmes, *M. Binnie, *P. R. Gittins, *J. R. Gough, *M. J. Peel, *J. B. Spargo, *R. Thomas, *P. O. Williams, *D. R. Sweetnam, *H. B. Eckstein, *J. S. McCormick, *T. B. Scott, J. W. B. Dalgleish, *H. F. Juckes, P. G. A. Irvine, *D. R. Bowsher, *J. M. Brown, *D. Butcher, *G. E. Heald, *T. M. Howell, *K. Last, *R. D. Montgomery, *R. H. Oram, *S. T. Pickles, *R. B. Prowse, *C. R. Robinson, J. L. Milligan, B. J. Muir, A. C. Townsend, *J. E. Dalby, *M. L. E. Espir, *J. N. Redfern, *P. R. V. Tomson, D. R. Pugh, J. H. Ross, *H. H. Broadhead, *G. N. St. J. Penney, J. S. W. Chambers, *C. R. Leeson, *T. S. Leeson, *A. G. Wallace, *P. Ll. Williams, K. E. Halnan, H. M. Michaelson, *P. G. I. Stovin, *S. E. Trickey, *M. S. Aldridge, *M. G. Rinsler, *A. C. Chovil, *T. D. W. Davies, *W. J. Wigfield, *J. P. Williams, A. D. Muirhead, *P. B. Brown, *Verity G. Wills, Frances E. Kirk, Dora W. Lemmon, Joan K. Perkins, Alison M. Richardson, *Mrs. Elizabeth R. Taylor, Mrs. Mary E. Kendrew, Mrs. Jane Lodwick, *E. Marley.

M.B.—*G. A. Mandow.

*By proxy.

UNIVERSITY OF LONDON

The following have been appointed, or nominated for appointment or reappointment, as representatives of the University on the governing bodies indicated in parentheses: Sir Archibald Gray (Bedford College); Sir Archibald Gray and Mr. J. B. Hunter (British Postgraduate Medical Federation); Mr. P. H. Mitchiner and Sir James Paterson Ross (Guy's Hospital Medical School); Professor L. P. Garrod (St. Mary's Hospital Medical School, Inoculation Committee, Wright-Fleming Institute); Dr. Ruth E. Proctor (Battersea Training College of Domestic Science).

The Municipal Borough of Luton has been added to the list of areas approved by the University for the purpose of instruction in public health administration for the Academic Postgraduate Diploma in Public Health.

The examination for the Postgraduate Diploma in Psychological Medicine (University Extension and Tutorial Classes Council) will be held for the last time in March–April, 1952. An Academic Postgraduate Diploma in Psychological Medicine has been instituted, the regulations for which may be obtained on application to the Academic Registrar, University of London, Senate House, London, W.C.1.

UNIVERSITY OF BIRMINGHAM

The opening ceremony of the new session of the Faculty of Medicine will take place in the Nurses' Recreation Hall, Nuffield House, Queen Elizabeth Hospital, Birmingham, on Tuesday, October 3, at 3 p.m., when Viscount Addison will distribute the prizes awarded for the session 1949–50 and will deliver an address to students.

UNIVERSITY OF BRISTOL

G. F. M. Hall has been approved at the examination for the degree of M.D.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the Royal College of Surgeons of England held on August 3, with the President, Sir Cecil Wakeley, in the chair, the Honorary Medal of the College was awarded to Lord Webb-Johnson in recognition of his many generous acts and

continued labours in the interests of the College throughout the eight years of his presidency.

The Gilbert Blane Medal was presented to Surgeon Commander E. B. Martin, R.N., for his research on naval aviation medicine.

A resolution of condolence was passed on the death of Mr. E. Cranmer Hughes, past member of the Court of Examiners.

Professor B. W. Windeyer was appointed a Hunterian Professor for 1951, for a lecture on "The Place of Radiotherapy in the Treatment of Malignant Disease."

Mr. R. J. Last, F.R.C.S., was appointed Professor of Applied Anatomy in the College.

Mr. L. E. C. Norbury was again nominated as the representative of the College on the Advisory Board on Nursing Education.

The Hallett Prize was awarded jointly to Tara Chandra (Lucknow University) and Malik Shaukat Hasan (Punjab University).

Diplomas of Fellowship were granted to R. H. Cram and O. V. Jooma.

Diplomas of Membership were granted to K. M. McFadyean and to the other 107 successful candidates whose names were printed in the report of the meeting of the Royal College of Physicians of London in the *Journal* of August 5 (p. 373) as recipients of the diploma of L.R.C.P.

Diplomas in Public Health and in Ophthalmic Medicine and Surgery were granted, jointly with the Royal College of Physicians of London, to the successful candidates whose names were printed in the report of the meeting of the Royal College of Physicians of London in the *Journal* of August 5 (p. 373).

Diplomas in Ophthalmology were granted, jointly with the Royal College of Physicians of London, to R. St. H. Warren and to the 21 other successful candidates whose names were printed in the report of the meeting of the Royal College of Physicians of London in the *Journal* of August 5 (p. 373).

The following hospitals were recognized under paragraph 23 of the F.R.C.S. regulations: Bury General Hospital (junior registrar for general surgery; junior registrar for orthopaedics; resident casualty officer; two house-surgeons (all for six months)). Coventry and Warwickshire Hospital (additional recognition of registrar and house-surgeon for otolaryngology). Hexham General Hospital (surgical registrar (for twelve months); first and second house-surgeons (general); orthopaedic registrar; and orthopaedic house-surgeon (all for six months)). Lister Hospital, Hitchin (surgical registrar (for twelve months); senior and junior house-surgeons (for six months)). Whipps Cross Hospital (three house-surgeons (for six months); house-surgeon to orthopaedic department (for six months)). Northampton General Hospital (registrar and house-surgeon for otolaryngology). Manfield Orthopaedic Hospital, Northampton (senior and junior orthopaedic registrars (for six months)). Rush Green Hospital, Romford (senior and surgical registrars (each for twelve months); and house-surgeon (for six months)). North Staffordshire Royal Infirmary (two house-surgeons; orthopaedic house-surgeon; ophthalmological and ear, nose, and throat house-surgeons; senior surgical registrar; assistant resident surgical officer; registrars in ophthalmology, orthopaedics, and ear, nose, and throat; junior orthopaedic registrar (all for six months only)). Sunderland Royal Infirmary (senior surgical registrar; second surgical registrar; registrar to ear, nose, and throat department; registrar to casualty department; registrar to orthopaedic department). Maelor General Hospital, Wrexham (two registrars and two house-surgeons (for six months only)). City General Hospital, York (two house-surgeons; orthopaedic registrar and orthopaedic house-surgeon (all for six months)).

CONJOINT BOARD IN SCOTLAND

The following candidates, having passed the final examinations, have been granted the diploma of L.R.C.P.Ed., L.R.C.S.Ed., L.R.F.P.S.Glas.: G. E. Aitken, Eleanor K. Althorp, R. F. Armstrong, J. G. Bhatt, A. F. Bushby, A. J. Cameron, J. Clougherty, A. P. Davidson, Elspeth G. Davie, Joy L. Di Marco, Audrey E. Evans, Margaret R. Farrell, T. A. Frewin, Eileen M. Gorman, Monica C. Grant, P. J. Halket, Mary T. Hill, G. E. Horseman, C. R. Hosein, J. D. Hughes, D. M. Johnstone, I. Kantor, H. L. Kinman, A. W. Laughland, Winifred A. Lloyd, I. N. H. Luck, C. N. McFarlane, G. C. McGlone, Margaret McKenzie, W. K. MacLean, J. F. Maguire, H. R. W. Miller, R. J. Misthry, G. T. D. Murray, Pauline A. Nock, Jean Poole, Hannah L. Pluss, J. B. M. Porter, Dorothy H. E. Ramsay, M. Raphael, Joan C. C. Reeves, Patricia M. Scanlan, Beatrice M. Sinclair, T. Slutsky, R. Sorkine, J. G. E. Smith, Margaret I. A. Smith, R. H. Thorp, G. A. Walters, A. White, A. C. Yelland.

UNIVERSITY OF MICHIGAN

In June the degree of Master of Public Health was conferred on Kenneth I. E. Macleod, M.B., Ch.B.

No. 33

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended August 19.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each Infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1950 (a)	(b)	(c)	(d)	(e)	1949 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Meningococcal infection	21	2	33	2	3	22	2	7	3	1
Deaths		—	—				—	—		
Diphtheria	31	—	15	1	4	59	8	23	1	6
Deaths	—	—	—	—	—	2	—	—	—	1
Dysentery	141	13	99	2	—	35	4	83	—	1
Deaths		—			—					—
Encephalitis, acute	13	1	—	1	—	3	—	1	—	—
Deaths		—		—			—			
Erysipelas			14	6	2			16	6	1
Deaths							—			
Infective enteritis or diarrhoea under 2 years					11					
Deaths	10		4	4	1	19	—	4	6	6
Measles*	5,529	362	79	85	22	2,120	158	57	96	37
Deaths†			—	—	—			—	—	—
Ophthalmia neonatorum	35	9	11		—	47	1	17	—	—
Deaths										
Paratyphoid fever	9	—	1 (B)		—	30	1	3 (B)	8 (B)	—
Deaths	—		—		—	—		—		—
Pneumonia, influenzal	233	8	1		2	245	13	2	2	6
Deaths (from influenza)‡	3	—	—	1	—	6	—	—	—	—
Pneumonia, primary			98	¶				127	20	
Deaths	76	9		2	9	103	11		4	8
Poliomyelitis, acute	550	38	65	8	18	295	35	14	1	2
Deaths§	26	2		1		14	2			
Puerperal fever		—	3				—	5		
Deaths										
Puerperal pyrexia‖	80	8	7	1	—	80	6	5	—	1
Deaths							—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	614	26	94	36	39	678	47	136	61	43
Deaths†			—	—	—			—	—	—
Smallpox	—	—	—		—	—	—	—	—	—
Deaths					—				—	—
Typhoid fever	9	—	—	1	—	6	3	1	2	1
Deaths	—	—	—		—	1	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths					—				—	—
Whooping-cough	3,939	336	220	61	33	1,637	82	41	118	82
Deaths	1	1	—	1	—	4	1	1	1	—
Deaths (0–1 year)	196	23	17	20	6	220	29	27	14	19
Deaths (excluding stillbirths)	3,886	577	481	166	101	3,910	635	513	167	108
Annual death rate (per 1,000 persons living)			9·7					10·3	10·3	
Live births	7,061	1150	821	323	209	7,087	1099	831	400	247
Annual rate per 1,000 persons living			16·5					16·7	24·8	
Stillbirths	179	15	20			188	29	21		
Rate per 1,000 total births (including stillborn)			24					25		

* Measles is not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

¶ Primary pneumonia no longer notifiable in Eire.

EPIDEMIOLOGICAL NOTES

Poliomyelitis

Notifications of poliomyelitis in the week ended August 26 were: paralytic, 369 (375); non-paralytic, 220 (175); total, 589 (550). The figures for the previous week are in parentheses. A decrease in paralytic cases of 6 was offset by an increase in the non-paralytic of 45, with a total increase for the week of 39 cases. A satisfactory feature is the increased percentage of non-paralytic cases from 32% in the preceding week to 37% in the week under review.

The main increases in total notifications occurred in the following county areas:

	Week Ended August 19	Week Ended August 26	Increase
Durham	9	31	22
Lancashire	29	44	15
Gloucester	26	38	12
Leicester	8	18	10
Yorks (E.R.)	1	11	10
Surrey	9	18	9
Dorset	6	13	7

Significant decreases occurred as follows:

	Week Ended August 19	Week Ended August 26	Decrease
Isle of Wight	19	6	13
Worcester	26	15	11
Warwickshire	47	39	8
Kent	17	9	8
Yorks (N.R.)	45	38	7

The following county areas have notified no cases in the period of three weeks up to August 26: Cambridge, Suffolk West, Cardigan, Radnor. In the same period the following notified one case only: Isle of Ely, Huntingdon, Soke of Peterborough, Anglesey, Brecknock.

The uncorrected notifications for the week in 1947, 1948, and 1949 corresponding to that under review were 676, 77, and 280 respectively.

Discussion of Table

In *England and Wales* decreases in the numbers of notifications were recorded for measles 891, scarlet fever 81, dysentery 70, acute pneumonia 23, diphtheria 18, while increases were reported for whooping-cough 517 and acute poliomyelitis 158.

The largest falls in the incidence of measles were Yorkshire West Riding 161, London 112, Hertfordshire 95. A small fall in the number of notifications of scarlet fever was reported from most areas. The notifications of diphtheria were the smallest ever recorded and were 8 below the previous lowest level of eight weeks ago. The chief feature of the returns of diphtheria during the week was a fall of 5 in London. The largest rises in the incidence of whooping-cough were London 83 and Middlesex 71.

The number of notifications of dysentery was the smallest for 36 weeks. A new outbreak involving 20 persons was reported during the week from Kent, Broadstairs and St. Peters U.D. The other large returns of dysentery were Lancashire 36 (Preston C.B. 9); Yorkshire West Riding 12; Durham 13.

The notifications of acute poliomyelitis were 158 more than in the previous week. The paralytic cases rose by 100 and the non-paralytic by 58. The largest returns during the week were Warwickshire 47 (Birmingham C.B. 24, Sutton Coldfield M.B. 6, Coventry C.B. 4, Meriden R.D. 4); Yorkshire West Riding 45 (Leeds C.B. 12, Wakefield C.B. 7, Bradford C.B. 4, Hemsworth R.D. 4); London 38 (Woolwich 7, Lewisham 6; the remaining cases were notified from 15 boroughs); Lancashire 29 (Liverpool C.B. 10, Manchester C.B. 5, Salford C.B. 5); Lincolnshire 28 (East Kesteven R.D. 10); Gloucestershire 26 (Bristol C.B. 18); Staffordshire 26 (Sedgley U.D. 4); Worcestershire 26 (Dudley C.B. 9, Worcester C.B. 8); Middlesex 23 (Hayes and Harlington U.D. 4); Essex 23 (Barking M.B. 4); Isle of Wight 19 (11 in Rural District); Kent 17; Northumberland 17 (Newcastle-upon-Tyne C.B. 9); Yorkshire North Riding 15 (Middlesbrough C.B. 4, Flaxton R.D. 4); Devonshire 14.

In *Scotland* decreases were recorded in the number of notifications of whooping-cough 36, measles 11, and rises were reported for dysentery 19, cerebrospinal fever 14. The chief centres of dysentery were Glasgow 60, Stirling county 10, and Edinburgh 8. The largest returns of acute poliomyelitis were Glasgow 22, Fife county 11, Dundee 4, Kirkcaldy 4.

In *Eire* a fall in the number of notifications was recorded for measles 64, scarlet fever 13, diarrhœa and enteritis 6. In Dublin C.B. the notifications of measles fell by 42, but a rise of 11 occurred in the notifications of whooping-cough.

In *Northern Ireland* a decline in incidence was recorded for measles 32 and scarlet fever 9, while a rise of 12 was reported for whooping-cough. The trends of these diseases were similar throughout the country. The chief returns for acute poliomyelitis were Down county 6, Belfast C.B. 5, and Antrim county 3.

Week Ending August 26

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 635, whooping-cough 3,725, diphtheria 41, measles 4,277, acute pneumonia 177, acute poliomyelitis 589, dysentery 137, paratyphoid fever 10, typhoid fever 11.

Medical News

The Boston Medical Library

On October 18 the Boston Medical Library will celebrate the seventy-fifth anniversary of its foundation. Two ground-floor rooms were opened as a library on Hamilton Place, for the use of Boston physicians, on Monday, October 18, 1875, with James Read Chadwick as librarian, E. H. Brigham as assistant librarian in charge, and Oliver Wendell Holmes as president of the new association. The present building was occupied in 1900. Long associated with the library is *The New England Journal of Medicine*, formerly the *Boston Medical and Surgical Journal*, and, more recently, the *Journal of Bone and Joint Surgery*. The Massachusetts Medical Society is housed in the present building and this year has acquired the adjacent property as a permanent home. To mark its birthday, the library will hold "open house" on October 18 with a scientific session and a dinner.

Alfred Adler Medical Society

The Alfred Adler Medical Society has been formed, and the following officers appointed: Professor Alexander Kennedy (president), Professor W. C. W. Nixon (vice-president), Dr. James Moore (chairman of council), Dr. E. N. Snowden and Dr. R. Strom-Olsen (vice-chairmen), Dr. A. R. Redfern (honorary secretary), and Dr. Donald Blair (honorary treasurer). The first meeting will be held at 8 p.m. on September 14 at 11, Chandos Street, London, W.C.2, when Dr. James Moore will deliver the inaugural address on "The Meaning of this Society."

Dominion Travelling Fellowships

The Nuffield Foundation is extending its scheme for Dominion travelling fellowships to Ceylon, India, and Pakistan. It already operates for Australia, Canada, South Africa, and New Zealand. The object of the fellowships is to advance the interests of the new Dominions and to strengthen their academic ties with the United Kingdom. Men and women graduates of outstanding ability and some postgraduate experience from the Dominions will gain further experience in Britain. The Nuffield Foundation will appoint Fellows on the recommendation of an advisory committee in each Dominion, the fellowship lasting one year and being valued at between £770 and £890. Travelling expenses will also be paid, as well as those of the Fellow's wife if he is married at the time of application. One fellowship in medicine will be awarded in Ceylon, and two in India. Three fellowships, the subjects for which are not yet chosen, will be awarded in Pakistan.

Touring U.S.A.

Professor W. C. W. Nixon, of University College Hospital, is leaving for a three-months tour of obstetric centres in the U.S.A., and on October 27 will give the DeLee Lecture at the Chicago Lying-in Hospital on "Uterine Action—Normal and Abnormal." The tour is sponsored by the Rockefeller Foundation.

COMING EVENTS

Society of Chemical Industry

A joint meeting of the Edinburgh Section and the Fine Chemicals Group of the Society of Chemical Industry will be held at Edinburgh on October 6–7. On October 6 Mr. F. Bergel, Ph.D., will speak at 10 a.m. on "The Biological and Therapeutic Significance of Organic Phosphates Occurring in Nature"; and on October 7 Professor G. F. Marrian, F.R.S., will deliver the third Lister Lecture on "The Adrenocortical Hormones." Particulars may be obtained from Mr. G. W. Walker, F.R.I.C., c/o T. and H. Smith, Ltd., Wheatfield Road, Edinburgh, 11.

Institute of Dermatology

The Institute of Dermatology will begin its winter course of lectures on October 3 at St. John's Hospital for Diseases of the Skin, Lisle Street, Leicester Square, London, W.C. The course will include special lecture demonstrations on medical mycology and a number of lectures on various branches of pathology relating to diseases of the skin.

Institute of Ophthalmology

The academic year 1950–1 of the Institute of Ophthalmology (University of London), (Judd Street, London, W.C.) will be inaugurated on Wednesday, October 4, at 4.30 p.m., with an address by Dr. W. Russell Brain, President of the Royal College of Physicians of London. The annual dinner of the institute will be held at Claridges Hotel, Brook Street, London, W., at 7.30 p.m. the same day. Past students of the institute and of Moorfields Westminster and Central Eye Hospital are invited to both these functions. Tickets for the annual dinner are 25s. each and may be obtained on application to the secretary of the institute at the above address.

Health of the Tuberculous

The Welfare Group of the Lambeth Civic Society will hold a conference on tuberculosis on September 30 at 3–9 p.m. Local organizations have been invited to discuss what can be done to help sufferers from tuberculosis. Anyone interested in the subject is invited, and should communicate with the secretary, Mr. J. S. Marrin, Welfare Group, Lambeth Civic Society, Lambeth Town Hall, Brixton Hill, London, S.W.2.

William Meredith Fletcher Shaw Memorial Lecture

Professor A. Leyland Robinson, emeritus professor of obstetrics and gynaecology in the University of Liverpool, will deliver the William Meredith Fletcher Shaw Memorial Lecture before the Royal College of Obstetricians and Gynaecologists, 58, Queen Anne Street, London, W., on Friday, September 29, at 2.30 p.m. His subject is "The Evolution of the Gynaecologist," and all medical practitioners who are interested are invited to attend. Admission is by ticket only, allotted in order of application, obtainable from the secretary of the college at the above address.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At University New Buildings (Anatomy Lecture Theatre), Edinburgh, September 12, 4.30 p.m., "*Sensitivity in Disease*," by Professor J. H. Biggart.

Thursday

ALFRED ADLER MEDICAL SOCIETY.—At 11, Chandos Street, Cavendish Square, London, W., September 14, 8 p.m., "*The Meaning of This Society*," Inaugural Address by the Chairman, Dr. James Moore.

LONDON COUNTY MEDICAL SOCIETY.—At St. Stephen's Hospital, Fulham Road, Chelsea, S.W., September 14, 3 p.m., clinical meeting.

APPOINTMENTS

Drs. F. A. Ibiam, O.B.E., and K. A. Abayomi have been reappointed Members of the Executive Council of Nigeria.

DAVIES, DONALD MAITLAND, M.D., M.R.C.P., Consultant Physician, Bury and Rossendale Group of Hospitals.

FLEMING, CHARLES, M.B., Ch.B., D.P.H., Medical Officer of Health for Rugeley Urban and Tutbury Rural Districts.

HUDSON, JOHN HARRAL, M.B., Ch.B., D.T.M.&H., D.P.H., additional post of Acting Part-time Medical Officer of Health, Borough of Dartford.

JARMAN, THOMAS FRANCIS, M.D., Consultant Chest Physician and Director of Mass Radiography, Wales, under Welsh Regional Hospital Board.

LIVERPOOL REGIONAL HOSPITAL BOARD.—The following senior medical staff appointments are announced: *Consultant Physician to Clatterbridge General Hospital*, F. J. Zacharias, M.D., M.R.C.P. *Consultant Orthopaedic Surgeon to Walton Hospital*, J. H. Redding, F.R.C.S.Ed. *Consultant Paediatrician to certain hospitals in Liverpool*, Anne E. McCandless, M.D., M.R.C.P. *Assistant Venereologist (whole-time) with duties at V.D. clinics in Liverpool*, F. Morgan, M.D. *Assistant Venereologist (whole-time) with duties at V.D. clinics in Birkenhead, Wallasey, and Liverpool*, T. Lyall, M.B., Ch.B. *Tuberculosis Medical Officer (whole-time) for North Liverpool area*, A. D. M. Hamilton, M.B., B.Ch., D.P.H. *Tuberculosis Medical Officer (whole-time) for Ormskirk area*, R. S. Nicholson, M.R.C.S., L.R.C.P.

LORANT, STEPHEN, M.D., Consultant Pathologist, Rochdale Group of Hospitals.

MITCHELL-HEGGS, FRANCIS S., M.B., F.R.C.S., F.R.C.S.Ed., Consultant Surgeon to Bury and Rossendale Group of Hospitals, Manchester Regional Hospital Board.

POWELL, K. J., M.B., B.S., D.A., Consultant Anaesthetist in the Exeter Clinical Area, South-western Regional Hospital Board.

REEVES, ANTHONY JOSEPH, M.D., D.P.H., County Medical Officer, Offaly, Eire.

ROBERTSON, GEORGE STUART, M.D., Chief Assistant School Medical Officer, Liverpool.

UNGLEY, GORDON, V.R.D., M.D., F.R.C.S., Consultant Surgeon to Lambeth Hospital, Brook Drive, London, S.E.

WILLIAMS, J. R. D., M.B., B.S., D.P.H., Assistant Venereologist at Ipswich, Bury St. Edmunds, and Lowestoft, East Anglian Regional Hospital Board.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bremner.—On August 22, 1950, at Newcastle-upon-Tyne, to Mary Bremner (formerly Cammock), M.B., Ch.B., and Alan E. Bremner, F.R.C.S.Ed., a son.

Murray.—On August 27, 1950, to Ailsa (formerly Tully), wife of Dr. Laurence H. Murray, Park Way, Rickmansworth, Herts, a son.

Perkins.—On August 4, 1950, at Stamford Hospital, Lincs, to Royce (formerly Thompson), wife of Squadron Leader I. M. Perkins, M.R.C.S., L.R.C.P., R.A.F., a daughter—Alison Villiers.

Tatlow.—On August 21, 1950, at Bristol, to Anne, wife of Dr. W. F. T. Tatlow, M.D., M.R.C.P., a son—John William Tissington.

Thomas.—On August 10, 1950, at 27, Welbeck Street, London, W., to Judith, wife of Trevor Meyrick Thomas, M.Chir., F.R.C.S., The Tudors, Farnborough, Kent, a son.

Watson.—On August 18, 1950, at Harrogate General Hospital, to Peggy (formerly Lowis), wife of Dr. J. E. Watson, 6, St. Roberts Road, Knaresborough, Yorks, a son.

Weiner.—On August 27, 1950, at the Radcliffe Infirmary, Oxford, to Marjorie (formerly Daw), wife of Dr. J. S. Weiner, a son.

Wilkie.—On August 12, 1950, at the Jessop Hospital, Sheffield, to Noreen (formerly Keer) and Dr. D. J. K. Wilkie, a daughter—Rosemary Elizabeth.

DEATHS

Agnew.—On August 30, 1950, at 44, Eastern Avenue, Reading, Berks, Henry Murray Agnew, L.R.C.P., L.R.C.S., D.P.H.

Badger.—On August 29, 1950, at his home, Guildford, Walter Spencer Badger, M.B., Ch.B., D.P.H., aged 78.

Boyd.—On August 17, 1950, at Gloucester, the result of an accident, Ringland Gilmore Boyd, M.C., M.B., B.Ch., aged 33.

Bushe.—On August 19, 1950, at Winchester, Charles Kendal Bushe, O.B.E., M.D., Surgeon Rear-Admiral, R.N., retired.

Cobbledick.—On August 20, 1950, at Coulsdon, Surrey, Arthur Stanbury Cobbledick, M.D., of London and Trevone, Cornwall, aged 79.

Crooks.—On August 31, 1950, at the General Hospital, Nottingham, Frederick Crooks, M.Ch., F.R.C.S.Ed., of 6, The Ropewalk, Nottingham, aged 63.

Dilling.—On August 18, 1950, at Thwaite, Coniston, Lancs, Walter James Dilling, M.B., Ch.B., aged 64.

Eccles.—On August 29, 1950, at Bon Accord, New Herrington, Co. Durham, Herbert Anderson Eccles, T.D., M.B., Ch.B.

Graham-Smith.—On August 30, 1950, at Forvie, Cambridge, George Stuart Graham-Smith M.D., F.R.S., aged 75.

Heaney.—On August 26 1950, at Chester, Francis James Strong Heaney, M.D., F.R.C.S.I., of 68, Rodney Street, Liverpool.

Hillier.—On August 18, 1950, at Birmingham, William Thomas Hillier, M.R.C.S., L.R.C.P., D.P.H., aged 74.

Low.—On August 24, 1950, at Calverley Lodge, Tunbridge Wells, Percy Charles Low, M.B., B.Ch., aged 88.

Milligan.—On August 25, 1950, at 9, North Audley Street, London, W., Wyndham Anstruther Milligan, M.D., F.R.C.S.Ed., aged 78.

Purser.—On August 22, 1950, at 55, Wimborne Road, Bournemouth, Robert Williamson Kinross Purser, M.R.C.S., L.R.C.P., M.R.C.O.G., aged 37.

Reid.—On August 19, 1950, at Edinburgh, Alexander Christie Reid, M.D., D.O., of 16, Pelham Road, Nottingham, aged 73.

Richardson.—On August 24, 1950, at Worthing Hospital, Horace Richardson, M.R.C.S., L.R.C.P.

Slade.—On August 16, 1950, at the Middlesex Hospital, Florence Slade, M.D., M.R.C.P., of 26, Church Row, Hampstead, London, N.W.

Strathearn.—On August 14, 1950, at his home, The Manor House, Verwood, Wimborne Minster Dorset, Sir John Calderwood Strathearn, C.B.E., M.D., F.R.C.S.Ed., Lieutenant-Colonel, R.A.M.C. (T.F.), retired, aged 71.

Twort.—On August 21, 1950, at Hammersmith Hospital, Charles Claud Twort, M.D., of "Romans," Roman Road, Southwick, Sussex.

Watt.—On July 24, 1950, Robert Watt, M.B., B.Ch., of 62, Crumlin Road, Belfast, aged 88.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Judging a Baby Show

Q.—*What points should I consider in judging a baby show? Granted that most of the babies are healthy, well nourished, and of normal weight, what other factors should I take into consideration?*

A.—This empirical art, productive of fierce maternal jealousies, requires an estimate of intelligence, social behaviour, physical state, beauty of appearance, and maternal care. On the whole the qualities which give aesthetic appeal go together with good health, and a largely subjective judgment is likely to be of most value. The features which make a fine baby and which can be assessed rapidly include brain, muscle, bone, and skin. Intelligence shows in an alert appearance and appropriate motor behaviour for age (any standard textbook on children will give a scale sufficiently simple and comprehensive for the purpose) and can be estimated quite well with a little practice; quiet and friendly behaviour will give evidence of social adaptation. Muscular development and tone can be tested simply and quickly. Bone structure can be seen best in legs and skull; generous allowance must be made for apparent bowing of the legs of plump babies. The skin provides essential evidence. The texture of a really healthy child's skin is unmistakable, and the presence of sun tan is at any rate evidence of sensible care. Scurf on the scalp and pustules on the face are misfortunes at least partly preventable by adequate use of soap and water. The hair is a further index of care: good condition is not to be achieved by five minutes' work before the show. Clothing deserves attention; it should be suitable and not excessive. The judge will probably find himself excluding a few babies by his olfactory sense, for the well-treated baby is a far more pleasant-smelling object than his less lucky neighbour, who tends to smell stale in spite of any amount of last-minute washing. Finally, it is probably fair to give a considerable number of marks for a pleasant, though not necessarily beautiful, face.

Family History

Q.—*Teachers and textbooks often assert the usefulness in diagnosis, treatment, and prognosis of the patient's family history. In so far as "usefulness" means practical benefit to the patient, is this assertion well founded? If so, in what kinds of case, and how does the benefit arise? Where can I find a critical analysis of the evidence purporting to establish such benefit in any fairly common condition?*

A.—There can be few physicians who would be prepared to jettison inquiry into the family history and to accept the patient as an isolated individual without antecedents, collaterals, or descendants. Nevertheless the questioner must not be disappointed if the "practical benefit" which results from such information is of a less obvious character than that which follows the drainage of an abscess. Perhaps its most easily appreciable value lies in those diseases of which the familial incidence is so high that the diagnosis is in serious doubt if relatives are not affected. Huntingdon's chorea, haemophilia, certain of the myopathies, acholuric jaundice, and the cerebellar ataxias provide examples. In many other disorders, of which essential hypertension, diabetes mellitus, peptic ulcer, pernicious anaemia, migraine, diseases of the gall-bladder, and the allergic states are instances, a family history is common; here diagnosis does not depend on this knowledge, but an indication of the prognosis may often be obtained. This is well shown by those families in which several members die of cerebral haemorrhage about the same age. Again, the prognosis of mental disorder, and in particular of depression, can be accurately assessed only in the light of the family history.

More important, if less easy to expound, is the part played by the family history in revealing to the physician the character and personality of his patient. No individual exists and develops in isolation; his parents and siblings in his early years, his wife and children in later years, people his environment, form his character, implant his habits, and shape his personality. It is a commonplace that the only son of a divorced couple will react to the stresses and strains of life differently from a member of a large and happy family. Without knowledge of the family history the doctor may be able to attach a suitable nosological label, but he will certainly have less insight into the man consulting him. His failure to seek this knowledge will deprive the patient of the "practical benefit" of advice founded on complete diagnosis, a term which Galen defined as "the thorough comprehension of things present."

Radium for Uterine Cancer

Q.—*Can you give me the latest figures for the five- and ten-year cure rates for carcinoma of the body of the uterus treated by radium? Is the modern tendency to treat this condition by radium in all cases, irrespective of the patient's fitness for operation?*

A.—The figures published in the 1948 report from Stockholm of the Radiumhemmet show that, of 264 cases treated during the years 1934–8, 171 (65%) were symptom-free after five years and 124 (47%) were symptom-free after ten years (Table XII, p. 114). The results are calculated by the method used in the League of Nations reports estimating the relative cure rate for cases of carcinoma of the cervix; they also take into account the patients operated upon after failure of radiological treatment. The series comprises all except the frankly untreatable cases, and therefore includes many cases inoperable at the time of institution of treatment by radium. The method used is the packing of the uterine cavity with many small sources of radium, the time being decided from the number of such sources and depending therefore on the size of the cavity, according to the method described by Heyman and published in the *British Journal of Radiology* (1947, **20**, 85). There are probably no better figures for a truly comparable series, and a study of the table referred to, which covers 980 cases from 1914 to 1943, indicates that since this method of treatment has been started the results have improved significantly. The general procedure in most countries is to operate on all operable cases, although a rational consideration of the evidence would suggest that treatment on the lines adopted in Stockholm will produce better results.

Chronic Synovitis of the Knee

Q.—*What is the modern treatment for chronic synovitis of the knee? Treatment has to be undertaken in an African village hospital where there are no facilities for laboratory investigations. I have tried repeated aspirations with replacement by penicillin, normal saline, and so forth, without success. The fluid continues to be yellowish and mucilaginous, and a course of N.A.B. injections has not been helpful.*

A.—The treatment of chronic swellings of the knee depends upon their cause. In general, the causes can be grouped into three classes: mechanical, inflammatory, and neoplastic. A fair idea of the group into which a particular case falls may be gained from a careful consideration of the history (noting particularly the circumstances of the onset, details of any injury, progress, etc.) and a full clinical examination. Swelling due to thickening of the synovial membrane, especially when associated with a local increase of temperature and limitation of all movements, suggests an inflammatory lesion (low-grade non-specific infection, tuberculosis, and rheumatoid arthritis are the commonest causes). Initial treatment should be by rest. On the other hand a recurrent effusion, varying in degree and unaccompanied by synovial thickening, suggests a mechanical cause (in a young adult a torn cartilage or loose body is usually responsible; in older patients the cause is almost always osteoarthritis). Treatment here is directed towards remedying the mechanical defect when possible, and this is followed by intensive muscle exercises. There are many cases, however, in which the diagnosis cannot be established without facilities for *x*-ray and laboratory

investigations, and if these are not available the problem becomes difficult. In such circumstances, if it is impracticable to transfer the patient to a centre where appropriate facilities are available, treatment should err on the side of caution. Thus in the case mentioned—though a definite opinion cannot be given because of the lack of information about the age of the patient, presence or absence of synovial thickening, local increase of temperature, movements, etc.—caution would suggest that the lesion be regarded as inflammatory and that treatment should be by resting the knee in a plaster case, from groin to ankle, for an initial period of at least six to eight weeks. Subsequently, if improvement in the local condition is apparent, a clinical trial out of plaster, with intensive quadriceps redevelopment exercises, should be advised; but should further signs of inflammatory reaction occur further rest may be required. In each individual case the programme to be adopted depends so much upon the clinical state and progress of the condition that it is not possible, in a short answer, to lay down any more definite plan of treatment.

Peribuccal Pigmentation

Q.—*A girl of 16, otherwise healthy, complains of brown pigmentation on either side of the upper lip. There is also some pigmentation of the brow. I should be grateful for suggestions about treating or bleaching the affected areas.*

A.—This peribuccal pigmentation, described by Brocq, is very common and certainly indicates some little derangement of endocrine function at puberty. This usually corrects itself, and active treatment may be unwise unless there is some other indication such as dysmenorrhoea. Small doses of oestrogens given for two or three weeks, starting with the first day of the period, may then be helpful. There is often waxing and waning of the pigmentation with each period. No attempts at removing or bleaching the pigmentation should be made. They are likely to damage the skin and are unnecessary, since the condition will clear.

Breast-feeding and Immunity

Q.—*Is there any evidence that breast-feeding produces any protection in the child from infectious diseases, particularly exanthemata, and, if so, in what way is this effected?*

A.—Passive transfer of antibody from mother to offspring occurs almost entirely via the placenta in the human species, whereas in the ruminants ingestion of the colostrum is the most important means of protection. Hence confusion often arises about the protection against infectious disease afforded by breast-feeding. There is no evidence that breast-fed babies are better protected against the exanthemata than are artificially fed infants; instead the degree and duration of immunity are closely correlated with the amount of antibody—e.g., diphtheria antitoxin—transferred from mother to foetus by way of the placenta. The relative immunity of the breast-fed baby to infantile enteritis is most probably due to factors other than the transfer of antibody.

Stilboestrol and Cancer of the Breast

Q.—*A woman aged 28 has obtained great relief from a prostrating dysmenorrhoea by the use of stilboestrol. The dose used two years ago was 1 mg. t.d.s. for the first fourteen days of the cycle. She now takes less than half that dose, with adequate relief. The patient's grandmother, mother, and maternal aunt have all had cancer of the breast. Is there any good reason to believe that stilboestrol might further predispose her to this condition? Apart from the stilboestrol, what are the risks of her contracting carcinoma of the breast, and at what age should one be particularly on the alert? Are there any recent advances in early diagnosis or prevention?*

A.—There is a strong family predisposition to cancer of the breast in this case, but it is impossible to assess the risk of this patient developing the disease; it would appear to be greater than for a woman without her antecedents. Although the disease can occur at a younger age, special attention should be given from 35 years onwards. As to early diagnosis, the outstanding sign is a lump in the breast, and it would be a wise precaution if the patient were examined at intervals of, say, six months. She should also feel her breasts from time to time and report immediately any lump which may be present. As to the prevention of cancer of the breast, women should avoid wearing brassieres which are unduly tight; uniform, even pressure should be applied to the breasts. It is wise to keep under observation a breast which is the site of an old abscess. After lactation the breasts should be emptied of all residual milk so that this is not allowed to stagnate. A blood-stained discharge from the nipple requires treatment, and special supervision should be given to patients who develop periductal fibrosis, cysts, and other forms of chronic mastitis. In view of the strong familial tendency to cancer of the breast it would seem that the taking of stilboestrol is inadvisable in this case, especially for so long. Could not the cause of the dysmenorrhoea be found and the appropriate treatment given? In any case, it would be wise to discontinue the use of stilboestrol.

NOTES AND COMMENTS

Corrections

Through an oversight, for which we must apologize, we included no summary of Professor V. F. Lambert's paper in our report (August 5, p. 356) of the meeting of the combined Sections of Oto-Rhino-Laryngology and Radiology at the Annual Meeting of the B.M.A. in Liverpool on July 20. Professor Lambert reviewed a series of 62 cases treated at the Manchester Christie Cancer Hospital and Holt Radium Institute since 1932 by means of the Finzi–Harmer radium technique, after fenestration of the thyroid cartilage. In the properly selected cases this treatment yielded a cure rate of 83%, a figure which included deaths from intercurrent disease as well. In the patients who died within the first three years the larynx was never well after the treatment. The cases in which the best results were obtained were those in which the growth was in the middle third of the cord. Anterior spread should not rule out treatment, but posterior spread was a definite contraindication to this type of therapy. The voice in all successfully treated cases was very good. Professor Lambert also reviewed his experience in the use of contact *x*-ray therapy for malignant growths limited to one side of the larynx according to the technique which he and T. A. Watson described in April, 1942. In a series of 53 cases, only 22 could be regarded as cured. In addition to the high percentage of failures morbidity was high, and consequently this method of treatment had now been abandoned. In the subsequent discussion Professor Lambert, who admitted that his views might not be shared by many of his surgical and radiological colleagues, also expressed the view that hyperkeratosis of the vocal cord should be regarded as a pre-malignant condition which should be treated by some form of irradiation therapy, even in the absence of clinical or microscopical evidence of malignant change. Once the condition crossed the narrow dividing line between the precancerous and the cancerous stage it tended to spread with great rapidity.

Professor E. W. Anderson, of the Department of Psychiatry, the Royal Infirmary, Manchester, has written to point out that we were wrong in stating in the *Journal* of August 26 (p. 516) that the training course in psychiatry at Manchester University is for one year. The course for the D.P.M. at this university now covers eight university terms.

Under the title "Professional Training of Army Medical Officers" (August 26, p. 517) we erroneously said that two revision courses in surgery a year are held at Westminster Hospital Medical School for senior officers of the Millbank College. In fact, officers attending the Senior Officers Postgraduate Course attend at the Westminster Hospital for clinical tuition in medicine and surgery during the second part of the course.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 2111. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 2111. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.